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*Infections of Infancy and Childhood*

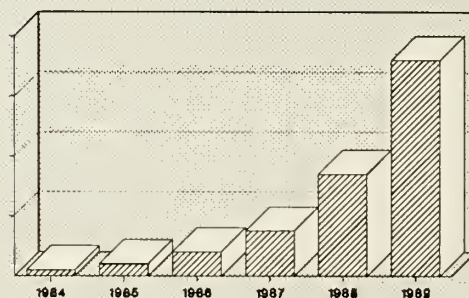


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**Cover:** This month's cover illustration is a painting entitled, "The Sick Child." The artist is Gabriel Metsu (1629-67).

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# EDITORIAL

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## Orphan Viruses in Search of Disease

In the lead article of this issue of the *Journal*, Singer and Oyer discuss the human parvovirus B19 and observe that "It was a virus searching for a disease until the early 1980s when it became associated with aplastic crises in patients suffering from chronic hemolytic anemia." This succession of events represents a new and curious reversal in the classical relationship between the clinical and the laboratory contributions to our understanding of human disease. Until about four decades ago, the customary sequence was: A disease, presumed to be infectious, was described clinically and its natural history documented; when its nosological uniqueness was verified an attempt was then made to isolate an organism and confirm (through rules sometimes called Koch's postulates) that the organism did indeed incite the disease.

First, the clinical definition of the disease; and only then the microbiological identification of the etiological agent.

Things began to change about 1948 when it was demonstrated that cultures of primate cells could be readily used to propagate certain viruses, and that these viruses then produced characteristically destructive (cytopathogenic) effects upon the masses of *in vitro* cell clusters. This substantially more simple laboratory strategy replaced the time-consuming and expensive method of

injecting unknown specimens into a variety of laboratory animals to determine whether a characteristic disease might in time develop. With this newer procedure research medicine possessed a powerful diagnostic tool, somewhat akin to the culture tubes and petri dishes used for bacterial isolation.

By the early 1950s, and before a poliomyelitis vaccine had been devised, many laboratories were engaged in widespread attempts to recover agents associated with crippling paralytic disease. They now used tissue culture methods and were able to process many more specimens expeditiously and at far reduced cost.

Various types of poliomyelitis virus were recovered by this broader screening capability. But in addition, however, newer strains of enteric virus sometimes turned up, similar in some ways to the poliomyelitis group and also associated occasionally with paralytic illness. For example, a strain of virus, distinguishable from poliomyelitis, was recovered from the stools of a few children suffering from acute paralysis. The virus was named Cocksackie, after the Hudson Valley town where these children lived.

Inevitably, stool specimens from clinically healthy subjects were also screened; and occasionally viral agents were isolated, many with biological characteristics placing them in the

family of enteric viruses (which now included the three poliomyelitis strains as well as the Cocksackie agents). But since these new isolates were not held responsible for any visible disease in humans or animals their role was left in abeyance — and hence they were designated as orphan viruses. The numbers of these "innocent" agents increased, and by 1955 they became collectively known as the "enteric cytopathogenic human orphan" viruses, or more colloquially, as the ECHO viruses.

In the ensuing decades many of the ECHO viruses have lost their pristine status and have become identified as the responsible agents for diverse disorders including forms of aseptic meningitis, respiratory syndromes, diarrheal disorders, encephalitis, paralytic disease, conjunctivitis and even cardiomyopathy.

There are now 34 strains of ECHO virus each associated with some disease manifestation in the human. (One of these strains, type 14, was first identified in Rhode Island.)

Thus, these particular orphan viruses are no longer orphaned. (Medical students, less impressed with established names than their professional elders, have often questioned the accuracy of the word, orphan, in this context. They point out that a virus is the *cause* rather than the *offspring* of a disease, and hence an orphan virus should more

properly be called a childless agent until it is shown to be associated with some offspring disease.)

The widespread screening of biological fluids has yielded many heretofore unrecognized viral agents which are not currently known to provoke human or animal disease. Among these newer candidates for the dubious distinction of causing human disease was the parvovirus B19, isolated in 1975 but orphaned for a decade until finally shown to be responsible for certain hematologic crises.

The numbers and strains of viruses pathogenic for humans now exceeds 400. And yet there still are numerous viral orphans, fully characterized, awaiting some investigative broker to marry them to a human disease.

And, on the other hand, are there infective diseases without identified inciting pathogens?

Evans<sup>1</sup> estimates that no causative agents have as yet been identified in 40% of appropriately studied cases of upper respiratory disease, 37% of cases of pharyngitis/tonsillitis, 30-50% of cases of pneumonitis, 72% of cases of encephalitis, 82% of cases of aseptic meningitis and 25% of instances of gastroenteritis. It appears that the mating dance between unassigned viruses and unresolved diseases will continue for many more years or decades.

This issue of the *Journal* reminds us that the ultimate roster of known infective agents is far from complete. The parvoviruses (from the Latin, *parvus*, meaning small) entered the clinical arena less than a decade ago. The respiratory syncytial virus (see article by Begue and Dennehy in this issue) was first recovered in 1956 from a chimpanzee suffering from coryza. A year later the virus was

isolated from infants with upper respiratory infection. It required another few decades of earnest epidemiologic study to realize that this allegedly rare pathogen was the chief cause of pneumonitis and bronchiolitis in human infancy and childhood.

To think that we will see the day when no new infectious agents await discovery is about as naive as expecting the day when there will be no new taxes.

Stanley M. Aronson, MD

<sup>1</sup> Evans, AS. *Viral infections of Humans*. Epidemiology and Control. Plenum Medical Book Co, New York, 1982.

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## EDITOR'S MAILBOX

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To the Editor:

In your editorial in the September 1990 issue of the **Rhode Island Medical Journal**, you write that "the three components of formal medical education — undergraduate, graduate and continuing — have expanded substantially in the last few decades." Subsequent articles in that issue address themselves to the first two components. I would like to speak to the third — continuing medical education.

Since the inception of the Brown University Program in Medicine, there has been an Office of Continuing Medical Education. Believing that practicing physicians are committed to lifelong learning, the CME Office sponsors professional education programs related to their needs and interests. Advances in biomedical technology occur so rapidly that CME's challenge is to provide instruction which allows physicians to maintain their intellectual and technical skills. The Brown CME Office is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. This voluntary accreditation reflects the CME Office's compliance with nationally determined educational standards.

In recent years there have been quality programs, directed by

medical school faculty, on subjects as far ranging as: brain cell implantation; the use of lasers in surgery (urology, otolaryngology, oncology, gynecology); advances in oncology/hematology; infant mental health; bone and mineral pathophysiology; diagnostic imaging; management of HIV infection and AIDS; cardiology; diabetes; tuberculosis; adolescent medicine; critical care medicine; trauma and trauma rehabilitation; geriatrics; and sleep disorders.

These programs, usually designed for local, community-based physicians, frequently attract specialty participants on a regional, national, and international level. Additional attend-

ance by allied health professionals broadens the audience of adults who seek continuing professional education and find it through Brown programs. During the 1988-89 academic year, Brown sponsored approximately 459 hours of continuing medical education programs which were attended by approximately 2244 practicing physicians.

Janice L. Miller, M.Ed.  
Director  
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*Editor's note: The Rhode Island Medical Society also acts as an accrediting organization for thirteen hospitals in Rhode Island to offer continuing medical education for physicians within the state.*

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# Fetal Parvovirus B19 Infections

Don B. Singer, MD  
Calvin E. Oyer, MD

***Parvovirus B19 . . . was a virus searching for a disease until the early 1980s when it was associated with aplastic crises in patients suffering from chronic hemolytic anemia.***

Parvovirus B19, the human parvovirus agent, was first identified in 1975 during screening of donated blood for hepatitis virus.<sup>1</sup> It was a virus searching for a disease until the early 1980s when it became associated with aplastic crises in patients suffering from chronic hemolytic anemia<sup>2</sup> and children with erythema infectiosum (fifth disease).<sup>3</sup> In 1983 and 1984, an extensive outbreak of human parvovirus-associated

erythema infectiosum occurred in northeast Scotland.<sup>4</sup> Six women had serologic evidence of infection during pregnancy. Of these, four delivered normal infants but two had stillborn hydropic fetuses.<sup>5</sup> Since that initial report, approximately 100 cases of fetal death due to parvovirus infection have been mentioned in the literature.<sup>6-18</sup>

## **Cases at Women and Infants Hospital**

Four cases of fetal parvovirus B19 infection have been reviewed at Women and Infants Hospital in the past 6 years (Table 1).

Marked hydrops and extramedullary erythropoiesis were found in all the cases. Nucleated precursors of red blood cells were easily identified in the placental fetal circulation (Figure 1). Even though autolysis was severe in the three cases with fetal death, nuclear inclusions were found in the nucleated red blood cells of the liver and other tissues (Figure 2). Hemosiderin deposits were prominent in the liver and spleen. In electron microscopic studies,

all four cases had readily visible, typical parvovirus inclusions in the nuclei of erythroid precursors (Figures 3 & 4).

## **Discussion**

Parvoviridae are single stranded DNA viruses that affect a wide range of animals, mostly mammals.<sup>19</sup> During replication the DNA of parvovirus B19 makes a hairpin turn at each end of the viral genome which results in a temporary double stranded appearance and also in a unique large fragment in restriction enzyme analysis that is not present in nonreplicating forms. This feature makes it possible to identify proliferating virus as opposed to dormant virus or portions of dead virus in tissue.<sup>19, 20</sup>

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## **ABBREVIATIONS USED:**

**BFU-e:** burst forming unit-erythroid  
**CFU-e:** colony forming unit-erythroid  
**DNA:** deoxyribonucleic acid  
**IgG:** immune globulin G  
**IgM:** immune globulin M

Each strain of parvovirus is infective only for a single host species; e.g., there is no cross infectivity between feline parvovirus, canine parvovirus or human parvovirus. Furthermore, the target cell in each species is different from target cells in other species. For example, the canine parvovirus infects the cardiac muscle and gastrointestinal tract of puppies. In cats, the bone marrow and gastrointestinal tract are affected. In other animals, the liver is the target organ. In humans, the nucleated red blood cell precursor is the main target cell. Erythroid colony-forming cells are inhibited by parvovirus B19 which is toxic for the BFU-e/CFU-e stages.<sup>20</sup> Reticulocytes are transiently reduced in normal subjects with parvovirus B19 infection and markedly reduced in those individuals with diseases characterized by pronounced reticulocytosis. Most of these patients have hemolytic diseases such as sickle cell disease, congenital spherocytosis, or thalassemia.<sup>19-22</sup> The bone marrow from such patients may show erythroid hypoplasia or aplasia. In the recovery stages, giant pronormoblasts are highly characteristic, if not diagnostic, of parvovirus infection.<sup>20, 23</sup>

Other patients who may suffer from chronic erythroid aplasia are those with poor host defense mechanisms and immunodeficiency diseases including Nezelof's disease and leukemia with immunosuppressive treatment.<sup>21, 22, 24</sup>

Other cells that are candidate target cells for parvovirus B19 infection include the brain, heart, liver and monocytes.<sup>13, 14, 25, 26</sup> Support for the direct involvement of the heart is obtained in one unpublished case described by Knisely and associates and the one described by Saint-Martin and associates.<sup>25</sup> Several other cases have had parvovirus B19 DNA

demonstrated in myocardium without significant symptoms referable to cardiac dysfunction.

Recently, Hartwig has reported a teratogenic effect from parvovirus B19. In an embryo or early fetus, unilateral microphthalmia and aphakia were found. There was also dysplasia of the sclera and retina. Skeletal muscles had eosinophilic degeneration and there were perivascular mononuclear infiltrates throughout the conceptus.<sup>27</sup>

In susceptible young children, parvovirus B19 passes quickly through a viremic stage to a stage of mild, usually clinically undetectable, bone marrow involvement with erythroid depression. This is followed in about two weeks by a rash characterized by red cheeks (the "slapped cheeks" appearance). The rash may be reticular and may spread to the neck, upper arms and shoulders. Such rashes tend to persist for a few days with gradual fading, only to recur when the skin is warm (as in a warm bath). The rash probably represents an immune response and is unrelated to direct infection of the skin by the virus. Mucous membranes are usually not affected or only minimally so. In adults, mild arthritic symptoms appear and these, too, are probably due to circulating immune complexes.

Figure 1. Placental villous capillary has fetal blood with two nucleated precursors of erythrocytes. (Arrows) Both have intranuclear inclusions characteristic of parvovirus B19. Hematoxylin and eosin stain. Original magnification — 100 ×.

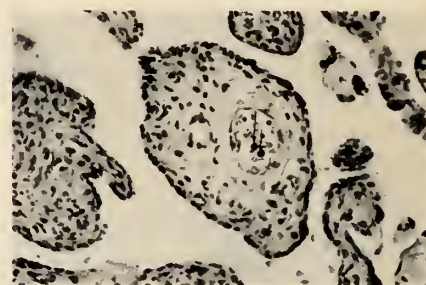


Figure 2. The autolyzed hepatic parenchyma has many nucleated precursors of erythrocytes and most of them have centronuclear inclusions. The nuclear chromatin is pushed to the periphery of the nucleus. (Arrows) Hematoxylin and eosin stain. Original magnification — 200 ×.

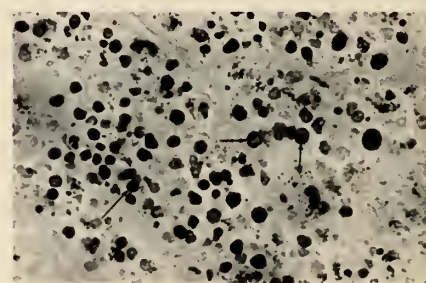


Table 1. Cases of Fetal Parvovirus Infection  
Women and Infants Hospital 1985-90

Case No.	Maternal Age/Parity	Gestation (Weeks)	Fetal Weight (grams)	Placental Weight (grams)	Comments
1	21/?	23	650	565	Maceration, hydrops
2	24/3	32	3500	800	Liveborn, hydrops survived 14 hours
3	22/3	23	575	460	Maceration, hydrops maternal antiparvovirus IgM positive
4	35/2	24	780	560	Maceration, hydrops maternal antiparvovirus IgM positive

Figure 3. Ultrastructure of infected nucleated erythroid precursor cell. The chromatin of the nucleus is pushed to the periphery and the center is replete with parvovirus particles. Original magnification 18,200  $\times$ .

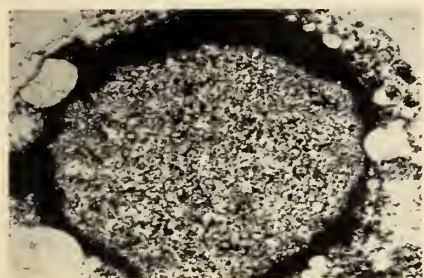
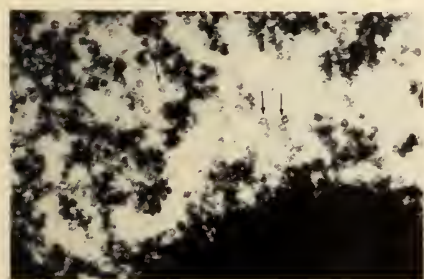


Figure 4. High magnification of viral particles showing 22-25 nanometer structures characteristic of parvovirus. Original magnification 120,000  $\times$ .



### Epidemiology of parvovirus B19

The human parvovirus is apparently transmitted parenterally through blood products, transplacentally from mother to fetus, and most commonly through respiratory secretions. The virus may also be transmitted by fomites but this has not been verified. As described above, infection is followed by viremia with bone marrow suppression and the early generation of IgM antibodies specific for the virus. Symptoms of fever, rash, arthritis, cough and, occasionally, coryza may appear in children after two weeks. The symptoms last for only a few days although the rash may recur as

described above. In adults, symptoms are minimal and consist mostly of arthritis. Some adults may also have a fleeting rash<sup>28</sup> (Table 2). In pregnancy, the infection may be devastating to the fetus.

***The human parvovirus is apparently transmitted parenterally through blood products, transplacentally from mother to fetus, and most commonly through respiratory secretions.***

In the United States, about 50-60% of the population are immune, having been exposed to the natural infection in childhood.<sup>28</sup> According to Gillespie *et al*, prior immunity was found in 58% of a population under study during an epidemic. Of the remaining 42%, 34% were at risk but were uninfected and 8% became infected. In a retrospective study by Kinney *et al*, similar results were obtained. Of those who were pregnant when initially infected, no significantly increased stillbirths or congenital malformations were detected among the offspring.<sup>11</sup>

In West Germany, Schwartz *et al* performed a prospective study and identified 42 patients with primary infections with parvovirus during pregnancy. Of these, three elected to terminate the pregnancy. The remaining 39 pregnancies resulted in 29 normal infants and 10 hydropic fetuses. Of these, seven died in utero. Three were treated with intrauterine transfusion and at the time of the report were healthy.<sup>16</sup>

In a small epidemic in Connecticut in 1985-86, Rodis *et al* evaluated nine gravidas of whom five were immune, four susceptible and three had hydropic fetuses. One normal infant was born among the four susceptible infected mothers. One of the hy-

dropic fetuses was also anencephalic.<sup>17</sup>

Overall, the apparent risk to mothers exposed to parvovirus equates to one per hundred or fewer having hydropic fetuses.<sup>11</sup> With this estimated rate, the risk of devastating and fatal disease in the developing conceptus is greater from parvovirus B19 than it is from cytomegalovirus, rubella, syphilis, and other infectious agents.<sup>5, 13</sup>

The risk to the early embryo has not been adequately studied although one case with embryopathy has been described.<sup>27</sup> It is of historic interest that Toolan, in a search for a human tissue cell line on which to culture tumor viruses, discovered a contaminant that we now know is parvovirus. The materials she used to establish the human cell line were from random conceptuses and placentas.<sup>29</sup> The rate of early pregnancy loss due to parvovirus is unknown but is currently under study.

### Fetal pathology

The most striking feature in a fetus severely infected with parvovirus B19 is generalized hydrops. The hydrops usually causes fetal death. Placentas may be five-six times heavier than normal due to the accumulation of watery fluid. Pallor is another feature since, in the pathogenesis of the human disease, destruction of red blood cell precursors is paramount. The liver and spleen may contain large amounts of hemosiderin, again on the basis of destruction of red blood cells.

Microscopically, fetal tissues may show a resurgence of nucleated blood cells as a response to the prior destruction. In such cases, marked erythroblastosis is found in placental and fetal tissues alike (Figures 1 & 2). The characteristic feature that distinguishes these nucleated erythroid

precursors from those of other erythroblastotic diseases is the characteristic nuclear inclusion. Inclusions are centered in the nuclei, stain blue with hematoxylin and eosin when small but become lilac to red with increasing size. With phloxine tartrazine stain, the large inclusions stain bright red. The nuclear chromatin is spread as a thin rim around the inclusions (Figure 2). The mean diameter of such nuclei is about 4 micrometers. A few cells have enormous, ballooned nuclei suggesting incipient lysis.<sup>7</sup>

**The most striking feature in a fetus severely infected with parvovirus B19 is generalized hydrops.**

By electron microscopic examination, the parvovirus particles are clustered in the center of the nuclei with peripheral condensation of the nuclear chromatin. The virions can be identified with high magnification. They are approximately 20-25 nanometers in diameter and, with good resolution, show a hexagonal outline. On occasion, crystallized viral particles may be identified.<sup>12</sup>

#### Methods of diagnosis

The first hint that parvovirus may be present in a pregnant woman is an elevated maternal serum alpha-fetoprotein.<sup>8</sup> This is a non-specific finding but may lead to the ultrasonic examination and diagnosis of hydrops fetalis. Specific identification of infection with parvovirus depends either on maternal serology or identifying the virus in the tissue or amniotic fluid. The serologic tests include both IgM and IgG.<sup>6</sup> The former indicates an active infection while the latter indicates prior infection or immunity.

Other means of making the di-

Table 2. Symptoms of Parvovirus B19 Infection

	Children	Adults
Rash	67%	13%
Fever	25%	15%
Cough	25%	—
Pharyngitis	25%	—
Coryza	17%	—
Arthritis	—	24%
Overall		
Symptoms	70%	35%
No Symptoms	30%	50%+

agnosis are by histologic and electron microscopic examination.<sup>12, 30</sup> Currently, methods are being developed for molecular DNA analysis using dot blot techniques on serum or Southern blot techniques after amplification by polymerase chain reaction. In situ techniques for identifying the virus are in the offing. (See accompanying article by Rogers *et al.*)

#### Therapy for fetal parvovirus B19 infection

If the viral infection has progressed to hydrops fetalis, intrauterine transfusions may be given in an attempt to save the fetus.<sup>16</sup> This may require repeated transfusion including postnatal transfusions for a successful outcome. The long term effects of the infection in terms of the possibility for permanent cardiac muscle damage, brain damage or liver damage are unknown.

**The long-term effects of the infection in terms of the possibility for permanent cardiac muscle damage, brain damage or liver damage are unknown.**

There is a rationale for immune globulin therapy since immunodeficient patients have been successfully treated with IgG injections.<sup>22</sup> It is also possible that immune serum with high titers of specific antiparvovirus B19 IgG

may become available and useful.

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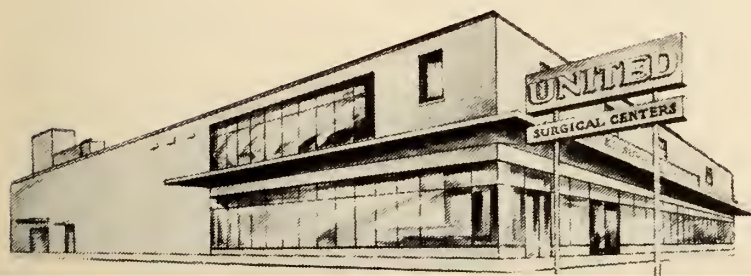


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# Detection of Parvovirus by DNA Analysis

Beverly Barton Rogers, MD  
Solida K. Mak, BS  
Linda Q. Covill, MT(ASCP)

**Detection of viral DNA in clinical samples has been achieved by using DNA probes specific for the virus in question.**

DNA technology has revolutionized diagnostic medicine, resulting in identification and characterization of a variety of inherited, neoplastic, and infectious diseases. Detection of viral DNA in clinical samples has been achieved by using DNA probes specific for the virus in question, and more recently amplification of viral DNA by the polymerase chain reaction (PCR) has resulted in identification of viral DNA in

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clinical samples without the necessity of hybridization.<sup>1, 2</sup> The techniques are particularly useful for organisms which require many days in culture for detection, and for viruses which are difficult to culture such as human immunodeficiency virus.<sup>3</sup>

The usual method of diagnosis of the disease caused by parvovirus B19 has been through clinical evaluation of the patient. For confirmation, serologic evaluation for antibody is available. In 1984, Cotmore and Tattersall cloned the genome of parvovirus B19 from the serum of an asymptomatic blood donor, making possible the development and use of molecular DNA techniques to diagnose infection.<sup>4</sup>

### "Dot Blot" Analysis

This type of DNA analysis is one of the more straightforward methods for detecting DNA in clinical material. It involves fixing DNA from the sample to a membrane and hybridizing with a probe (portion of DNA homologous to the unique nucleotide sequence of the virus). The probe is radiolabelled with <sup>32</sup>P and an autoradiogram is done as the final step. This technique has been used to detect parvovirus B19

from serum of persons with hemolytic anemias suffering from aplastic crises.<sup>5</sup> In one study, sera were examined from 37 patients. Parvovirus B19 genome was detected in serum as early as 11 days before and as late as 11 days after the clinical onset of symptoms. This dot blot procedure is capable of detecting 0.3 picograms (pg) of viral DNA, equivalent to 10<sup>4</sup> viral particles.

### Polymerase Chain Reaction Amplification

One of the latest technical advances using DNA technology has been the polymerase chain reaction (PCR). The PCR is an *in vitro* system which rapidly amplifies DNA up to a million fold, thus markedly increasing the sensitivity of the DNA assay.<sup>6</sup> Because it is also a rapid test, it frequently does not require hybridization for viral detection.

**ABBREVIATIONS USED:**  
DNA: deoxyribonucleic acid  
fg: femtogram  
IgM: immune globulin M  
PCR: polymerase chain reaction  
pg: picogram

There are basically four components to each PCR reaction:

1. DNA polymerase
2. Free DNA nucleotides
3. Primers (synthetic DNA) specific to the target DNA
4. Target (or template) DNA — in this case parvovirus B19

The principle behind the PCR involves a DNA polymerase (Taq polymerase) which synthesizes DNA artificially. The enzyme recognizes when a DNA molecule is partially double-stranded and partially single-stranded, as would occur in DNA replication or repair, and will "fill in the gaps" (Fig. 1). It uses free nucleotides placed in the solution to synthesize double stranded DNA from partially single-stranded DNA.

**... the target DNA can be amplified up to a million times making the detection of minute amounts of virus possible.**

For the Taq polymerase to synthesize DNA, certain conditions need to be met. First, the DNA needs to be in a partially double-stranded, partially single-stranded form. This is artificially done by denaturing the DNA (normally occurring in a double-stranded form) at high temperatures to produce single-stranded DNA. The temperature is then lowered so that short strands of synthetic DNA (called primers), placed into the test solution, can attach to the DNA of interest. Because the primers are approximately 25 nucleotides long and the DNA of interest is hundreds to thousands of nucleotides long, the DNA will be in a partially double-stranded, partially single-stranded form after the primers anneal (Fig. 2). The primers are chosen with specific sequences such that they will attach only to the DNA of interest, in this case parvovirus B19 DNA.

Figure 1. The Taq enzyme attaches the nucleotide to the 3'-OH region of the growing DNA chain, liberating two phosphorous groups in the process.

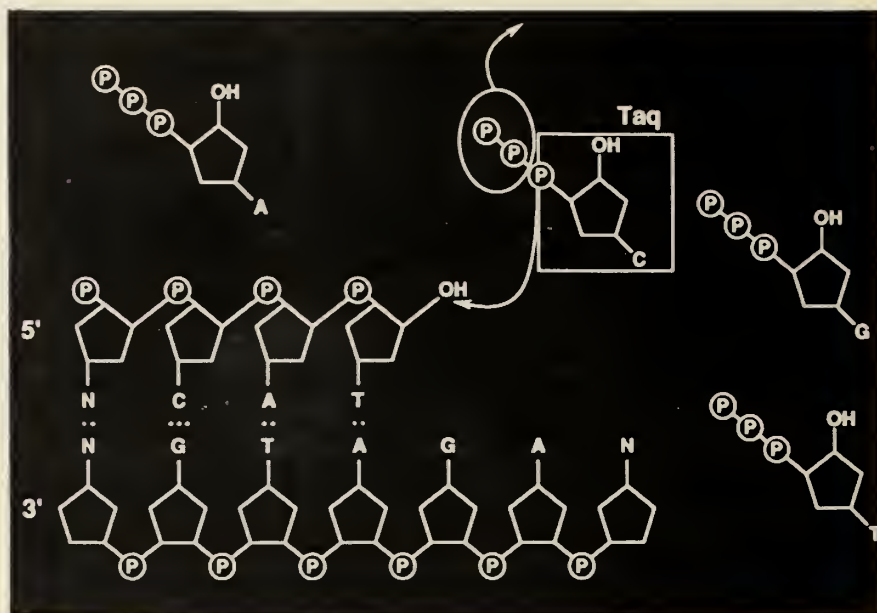


Figure 2. The PCR involves sequential rounds of denaturation of double strands of DNA to single strands, followed by annealing of complementary primers, and extension by Taq polymerase resulting in doubling of DNA with each cycle.

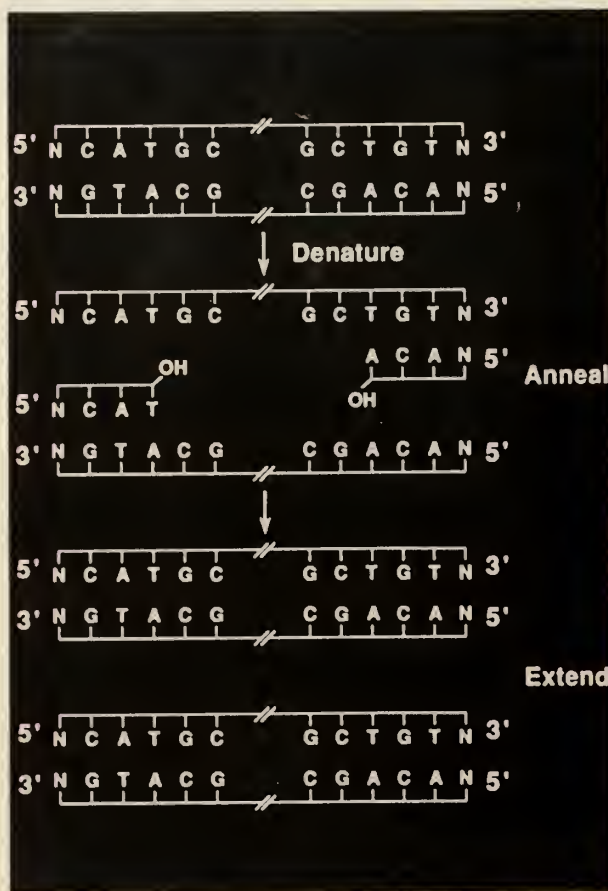


Figure 3. a. The 104 nucleotide product of amplified parvovirus DNA has a central sequence of four nucleotides which is cut by RsaI restriction enzyme, resulting in two 52 nucleotide fragments after cleavage. b. A photograph of the parvovirus amplification product using gel electrophoresis shows the 104 nucleotide fragment (closed arrow, lane 2) and a 52 nucleotide band (actually 2 fragments) after cleavage with RsaI (open arrow, lane 3). Lanes 1 and 4 are molecular weight markers used as size standards.

After the primers attach the temperature is raised so the Taq polymerase, which works best at high temperatures, can "fill in" (extend) the single-stranded DNA with the free nucleotides.

One can see from Fig. 2 that at the end of each cycle, there is twice as much DNA as at the beginning of the cycle. Multiple cycles of denaturation, annealing, and extension are carried out resulting in doubling of the DNA each time, allowing for amplification of the target DNA  $2^n$  times with "n" being the number of cycles. Practically speaking, the target DNA can be amplified up to a million times making the detection of minute amounts of virus possible.

The final amplified product is subjected to gel electrophoresis, and a dye is placed into the electrophoresis chamber which at-

taches to DNA and fluoresces, allowing visual detection of the amplified product. Because non-specific amplification of DNA can occur, it is necessary to confirm that the amplified product is specific, which can be done by cleaving the amplified product with a restriction enzyme. Restriction enzymes cut at specific sites in DNA, recognizing particular nucleotide sequences.

We have done the PCR for parvovirus in our laboratory on a section of paraffin-embedded, formalin-fixed placenta which had inclusions typical of parvovirus. The results are shown in Fig. 3. The primers have been previously published<sup>7</sup> and result in amplification of parvovirus B19 to give a 104 nucleotide fragment with an *RsaI* restriction enzyme site in the middle. The amplified product is shown schematically in 3a, and an electrophoresis with direct visualization of the DNA is shown in 3b (lane 2, closed arrow). *RsaI* will cleave the nucleotide sequence GTAC, present in the middle of the amplified fragment. This results in two 52 nucleotide fragments (Fig. 3a), seen as a single band in 3b (lane 3, open arrow). The upper band in lanes 2 and 3 is most likely an amplification by-product.

#### Application of the PCR to Parvovirus B19

The PCR has been used to detect parvovirus B19 DNA in sera and tissues. Salimans *et al* compared the PCR to dot blot hybridization and found it to be more sensitive in detecting viral DNA. With the primers in use in that laboratory, the anticipated sensitivity was 1-10 femtograms (fg) of DNA which corresponds to 100 viral particles. These investigators used the PCR to analyze tissues from a fetus known to be positive for the virus, and were able to detect virus in the liver, heart, lung and,

to a lesser extent, thymus and brain.<sup>8</sup> This type of technology makes analysis of paraffin-embedded tissues possible in a retrospective fashion.

The PCR has also been used to detect parvovirus B19 DNA in sera from individuals recently infected with the virus. In patients with a positive IgM antibody titer to parvovirus B19, 63% were found to be positive by the PCR.<sup>9</sup> Alternatively, 99% of sera from presumably uninfected individuals were negative by the PCR. The one case which was positive was felt to be a person with asymptomatic viremia. Fresh placental tissues from women who had proven parvovirus B19 infections during pregnancy but who gave birth to healthy infants were also examined, and 83% were found to be positive for parvovirus B19 DNA.

**Over the next few years, DNA technology will become increasingly available and may be among the routine diagnostic tests in the future.**

Not only can the PCR be used to detect parvovirus B19 DNA in sera and fresh tissue, but it is also useful in analysis of paraffin-embedded, formalin-fixed tissue. As is shown in Fig. 3, DNA from formalin-fixed placental tissue showed a specific parvovirus B19 band after amplification. This illustrates the possibility of retrospective studies using autopsy or surgical material.

#### Summary

DNA technology has been used to diagnose parvovirus B19 infection in clinical samples. The tests are specific and can attain a high degree of sensitivity, particularly when using PCR amplification. Over the next few years, DNA technology will become increas-



ingly available and may be among the routine diagnostic tests in the future.

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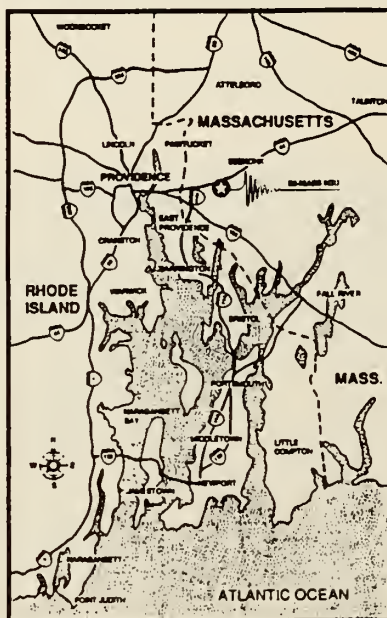
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# Respiratory Syncytial Virus Infections at Rhode Island Hospital: Use of Ribavirin

Rodolfo E. Begue, MD  
Penelope H. Dennehy, MD

**Half a million RSV-infected children (each year) present with lower respiratory infections such as bronchiolitis or pneumonia and fifty thousand require hospitalization.**

Since its discovery in 1957,<sup>1</sup> respiratory syncytial virus (RSV) has been recognized as a major cause of respiratory disease in young children. In the United States two million children under one year of age are infected with RSV every year. Half a million RSV-infected children present with lower respiratory tract infections such as bronchiolitis or pneumonia and fifty thousand require hospitalization.<sup>2</sup> Virtually all children in

the United States are infected with RSV at least once by 24 months of age and approximately 50% will experience a second episode of infection.<sup>3</sup>

The mortality from RSV in the general pediatric population is 0.005% but can reach 73% in certain high risk groups. Groups that should be recognized as at increased risk for severe RSV infection and consequent high mortality are those with: congenital heart disease,<sup>4</sup> bronchopulmonary dysplasia,<sup>5</sup> cystic fibrosis,<sup>6</sup> immunodeficiency state<sup>7</sup> and age younger than 6 weeks.<sup>8</sup>

Antiviral therapy is currently available for RSV infection. Ribavirin (Virazole) was released in 1986 and is approved for use in RSV infections. The drug is delivered by the aerosol route into a mist tent, oxyhood or endotracheal tube. A number of beneficial effects have been described with the use of aerosolized ribavirin for the treatment of RSV infection including: reduction in virus titers, shortening of the

duration of virus shedding, subjective improvement in the illness score and objective improvement in the oxygen saturation.<sup>9</sup> This salutary effect is seen in normal infants infected with RSV as well as in those with cardiopulmonary disease.<sup>10, 11</sup> However ribavirin therapy has not affected the clinical symptoms of fever or wheezing or changed the duration of hospitalization. The effect of ribavirin therapy on mortality still remains to be determined. The Committee on Infectious Disease of the American Academy of Pediatrics has outlined recommen-

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## ABBREVIATIONS USED:

ANOVA: analysis of variance  
BPD: bronchopulmonary dysplasia  
CHD: congenital heart disease  
DFA: direct fluorescent antibody  
ICU: intensive care unit  
PT: prematurity  
RR: respiratory rate  
RSV: respiratory syncytial virus

dations for the use of ribavirin in the treatment of RSV infections in children with severe disease or those with underlying conditions which increase the risk of serious RSV infection.<sup>12</sup>

No toxicity has been documented with aerosolized ribavirin but a number of potential side effects have created concern about the use of this drug. Potential adverse reactions in patients receiving ribavirin include: mild, short-lived bronchospasm, occurring in the first 8-10 hours of drug administration; rash and skin irritation as a result of prolonged contact with the drug; and precipitation of the drug in the endotracheal tube of ventilated patients, which can be avoided by adequate humidification and heating of the ventilator tubing and the use of filters.<sup>13</sup>

Health care workers are potentially exposed to high environmental levels of ribavirin during nebulization. The drug has been detected in the red blood cells of only one caretaker despite the fact the ribavirin is known to concentrate in erythrocytes.<sup>14, 15</sup> Adverse effects such as bronchospasm, headaches and eye irritation have been noted in health care providers exposed to ribavirin but these effects have been mild.<sup>16</sup> Teratogenicity and mutagenicity have been shown in laboratory animals treated with large doses of ribavirin raising concerns about reproductive risks to health care workers although no teratogenicity has been documented in humans or higher primates.<sup>17</sup>

The purpose of this study was a retrospective review of cases of RSV infection seen at Rhode Island Hospital during the three years after the release of ribavirin to assess the impact of concerns about toxicity on the use of ribavirin, and the resulting effect, if any, on the course and outcome of RSV-infected patients.

## Methods

A chart review of patients admitted to Rhode Island Hospital testing positive for RSV by culture or DFA during the period June 1987 to May 1990 was performed. A total of 2265 patients were tested by the Virology Laboratory at Rhode Island Hospital during the study period, 885 (39%) had a positive test for RSV and 322 were hospitalized at our institution. Of the 322 patients 317 had charts available for review.

***... during the period June 1987 to May 1990 ... a total of 2265 patients were tested ... 885 had a positive test for RSV and 322 were hospitalized at our institution.***

The information collected from each chart included: age, date of admission, length of stay, underlying disease, presenting syndrome, need for and length of intensive care and/or mechanical ventilation, use of ribavirin, indication for the use of ribavirin (according to Table 1) and complications of treatment. For the purpose of this review, the following terms are defined:

- Prematurity (PT): a patient born equal to or less than 36 weeks gestational age and under one year of age at the time of RSV infection.
- Bronchopulmonary dysplasia (BPD): as diagnosed by clinical and radiological picture during the neonatal period, and requiring oxygen, bronchodilators or diuretics for the 3 months prior to the RSV infection.
- Pneumonia: focal infiltrates on chest roentgenogram.
- Severity: RR greater than 80/minute, pO<sub>2</sub> less than 65 mmHg, pCO<sub>2</sub> greater than 40

mmHg and/or clinically in distress (retractions, cyanosis, etc).

Patients with prematurity and bronchopulmonary dysplasia or prematurity and congenital heart disease as underlying conditions were classified as BPD or CHD respectively. Patients with prematurity as sole underlying condition were classified as PT. Clinical presentation was recorded according to the most prominent syndrome pertinent to the RSV infection as judged by the reviewer.

Appropriateness of ribavirin therapy was judged by adherence to the guidelines (Table 1) recommended by The Committee on Infectious Disease of the American Academy of Pediatrics as modified by McIntosh.<sup>18</sup> During the period of study recommendations for the use of ribavirin at Rhode Island Hospital were issued at the beginning of the second and third years of surveillance. For the 1988-1989 season recommendations included: use in high risk patients with RSV infection including those with CHD, BPD, chronic pulmonary diseases or immunodeficiency and in normal children with severe RSV infection plus exclusion of pregnant health care workers from care of infected patients. In addition to the recommendations made during the second season guidelines for ribavirin use in 1989-1990 provided further protection for health care workers by the use of a double tent system to contain aerosolized drug, shutting off the small particle generator and the wearing of masks when the caretaker entered the tent.

Analysis of Variance or t test for numerical variables and chi square or contingency table comparisons for categorical variables among groups of patients were performed. A value of  $p < 0.05$  was considered significant.

## Results

### *Epidemiology of RSV Infections:*

RSV infections showed a typical seasonal distribution during the three years of the study (Figure 1), first appearing in November-December, peaking in January-February and disappearing in April-May until the next season. There were 71 RSV-infected patients during the second season of surveillance fewer than the 127 and 119 hospitalized during the first and third seasons respectively ( $p = 0.0002$ , ANOVA). This biennial pattern of major epidemics alternating with less severe epidemics has been consistently seen over the past six years at our institution as well as in other institutions in the United States.

### *Demographics:*

The mean age at admission and the presenting clinical syndromes were similar for all three years of study (Table 2). The av-

**Table 1. Guidelines for the Use of Aerosolized Ribavirin in the Treatment of RSV Infection**

- I. Patients with lower respiratory tract disease who have:
  - Severe Congenital Heart Disease.
  - Severe BPD and other chronic lung conditions.
  - Post operative cardiac surgery.
- II. Use when progressive respiratory involvement is seen in patients with:
  - Moderate Congenital Heart Disease.
  - Symptomatic BPD and Cystic Fibrosis.
  - T cell defects, recipient of recent transplant, cancer chemotherapy.
  - ? prematurity and age less than 6 weeks.
- III. In any child who is severely hypoxic (paO<sub>2</sub> less than 65 mmHg) or tiring and relatively hypercapnic (pCO<sub>2</sub> greater than 40 mmHg).

(From McIntosh, reference 18)

erage age at admission was 7.3 months with a range of 0.1-84 months. Bronchiolitis and upper respiratory infections were the most common presenting clinical syndromes followed by pneumonia and apnea.

The three RSV seasons differed in the proportion of patients with underlying conditions. The first surveillance season had more patients with an underlying disease,

64 of 127 (50%), as compared to the second and third seasons, 23 of 71 (32%) and 39 of 119 (33%) respectively ( $p = 0.01$ , contingency table). Prematurity (PT) alone was the most common underlying condition, followed by associated CHD and BPD but the proportion of patients with these conditions did not differ between the seasons. Patients with other conditions accounted for the dif-

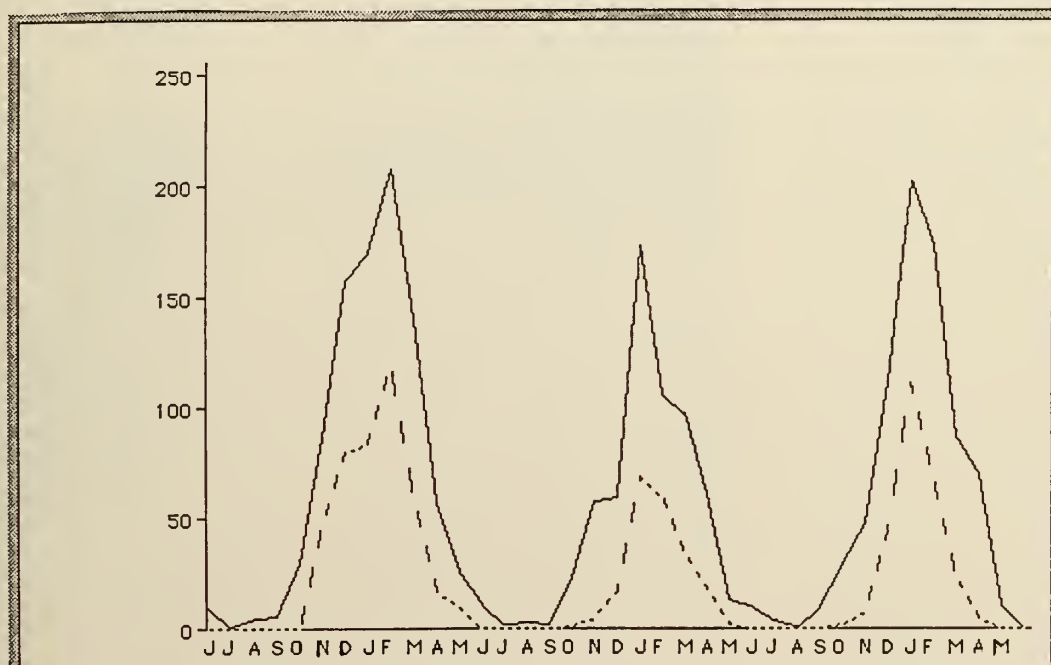


Figure 1. RSV cases as diagnosed at Rhode Island Hospital. First season: 1987-1988; second season: 1988-1989; third season: 1989-1990.  
 — : number of patients evaluated for RSV.  
 --- : number of positive cases for RSV.

Table 2. Characteristics of Children with RSV Infection Hospitalized at Rhode Island Hospital, 1987-1990

	Study Year			P Value
	1987-1988	1988-1989	1989-1990	
Mean age (mo.) $\pm$ standard error	8.2 $\pm$ 1.2	6.1 $\pm$ 1.1	7.1 $\pm$ 0.8	NS*
Clinical Syndrome				
Bronchiolitis	59 (46%)	36 (51%)	63 (53%)	NS
Upper respiratory infection	36 (28%)	24 (34%)	33 (28%)	NS
Pneumonia	18 (14%)	7 (10%)	10 (9%)	NS
Apnea	9 (7%)	3 (4%)	9 (7%)	NS
Sepsis	5 (4%)	1 (1%)	4 (3%)	NS
Underlying Illness				
Prematurity	14 (11%)	10 (14%)	18 (15%)	NS
Bronchopulmonary dysplasia	10 (8%)	1 (1%)	5 (4%)	NS
Congenital Heart Disease	11 (9%)	4 (6%)	4 (3%)	NS
Other	28 (22%)	8 (11%)	12 (10%)	0.02
None	64 (50%)	48 (68%)	80 (67%)	0.01

\*: Not significant

ference between the first and second and third seasons ( $p = 0.02$ , contingency table). These conditions included asthma, cystic fibrosis, obstructive sleep apnea, repeated aspiration pneumonia, immunodeficiency states, chronic neurologic conditions and metabolic/genetic diseases.

#### *Antiviral Treatment and Clinical Outcome:*

Forty-nine (15%) of the 317 patients with RSV infection received ribavirin therapy. Thirty-nine (80%) of those treated had underlying diseases known to be associated with increased severity of infection. The most frequent indications for ribavirin use were pulmonary (15) or cardiac (14) disease, followed by severe disease in the normal child (6) and immunodeficiency (4). When the criteria listed in Table 1 were applied, 10 (20%) of the 49 patients treated with ribavirin should not have been treated. All 10 patients were treated during the first season; four had apnea, four were less than 6 weeks of age and two had no underlying condition and mild disease.

There was a decline in the use of ribavirin over the three seasons of surveillance (Figure 2). During the first season 39 of 127 (31%)

patients received ribavirin, as opposed to 7 of 71 (10%) during the second season and 3 of 119 (2.5%) during the third season ( $p = 0.0001$ , contingency table). The decreasing trend in the use of ribavirin was seen not only for the infected cohort as a whole but also for those patients with underlying diseases.

***We believe that because of potential side effects ribavirin should be reserved for high risk groups who deteriorate despite optimal supportive care.***

Ribavirin was not given to 268 (85%) of the 317 patients with RSV infection. Of the 268 untreated patients 182 (68%) had no underlying conditions, 38 (14%) were preterm infants, 5 (2%) had CHD, 4 (1%) had BPD, and 39 (15%) had other underlying conditions. In order to assess the impact of ribavirin therapy the clinical outcome of untreated patients was compared with that of children receiving ribavirin. Eleven untreated patients with no underlying condition but severe RSV disease are compared with 6 normal children with severe disease receiving ribavirin in Table 3.

Length of stay and use and duration of intensive care and intubation were not significantly different although the ribavirin group fared slightly better in all aspects of comparison. Similar analysis of treated and untreated patients with CHD and BPD also revealed no significant differences in the clinical outcomes. The 18 patients with CHD had an average length of stay of  $7.1 \pm 1.2$  days, and spent an average of  $1.9 \pm 0.9$  days in the ICU and  $0.8 \pm 0.6$  days intubated. The 15 with BPD were hospitalized a mean of  $9.9 \pm 1.8$  days, spent  $4.6 \pm 1.9$  days in intensive care and  $2.7 \pm 1.5$  days intubated.

Three patients died (mortality rate 0.9%); one of unrelated causes one month after the RSV infection, and the other two within 9 and 12 days of diagnosis. The latter two patients were started on ribavirin but developed bronchospasm and the drug was discontinued.

Use of ribavirin was associated with complications in 6 cases, five were bronchospastic episodes (three of them severe enough to preclude use of the medication) and one episode of plugging of the mechanical ventilator system.

Figure 2: Percentage of Children with RSV Infections Treated with Ribavirin. Rhode Island Hospital, 1987-1990

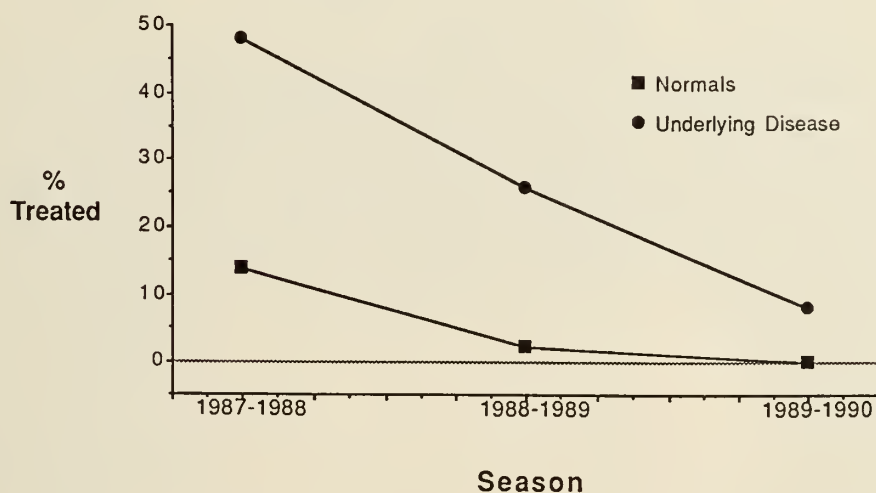


Table 3. Effect of Ribavirin Treatment on the Clinical Outcome of Normal Children with Severe RSV Infection Hospitalized at Rhode Island Hospital 1987-1990

	Treated n = 6	Untreated n = 11	P Value
Length of Stay (days) $\pm$ standard error	6.3 $\pm$ 1.0	8.4 $\pm$ 1.0	NS*
ICU (no. and %)	4 (67%)	8 (73%)	NS
ICU (days) $\pm$ standard error	1.3 $\pm$ 0.5	2.6 $\pm$ 0.7	NS
Intubation (no. and %)	0	4 (36%)	NS
Intubation (days) $\pm$ standard error	0	1.5 $\pm$ 0.7	NS
Clinical Syndrome			
Pneumonia	3 (50%)	4 (36%)	NS
Bronchiolitis	3 (50%)	7 (64%)	

\*: Not significant

## Discussion

Since a theoretical risk of teratogenicity exists and high environmental levels of ribavirin have been documented when the drug is nebulized into a mist tent<sup>15</sup> our hospital adopted guidelines during the 1988-89 RSV season to minimize the exposure of health care workers to ribavirin aerosol. These recommendations were broadened during the 1989-1990 season to provide further protection. Despite the attempts to limit exposure concern still existed about the potential adverse effects in health care personnel exposed to the drug. The major decrease in the use of ribavirin for RSV infection occurred at our institution in conjunction with the increasing concerns about ribavirin toxicity.

Despite the decreasing trend in the use of ribavirin the results of this review suggest that the decrease has not been detrimental in the clinical outcome of RSV in-

fectured patients. Length of hospitalization and need for intubation and intensive care were slightly longer in untreated patients without underlying disease but not significantly so. A larger number of patients would be needed to ascertain whether the trend in fewer days of intensive care, intubation or hospitalization seen in our survey is real. For patients with BPD and CHD ribavirin had no discernible effects on outcome. Three deaths occurred but the mortality was low for the three seasons (0.8%, 2.8% and 0% respectively) despite the changing trend in the use of ribavirin.

We believe that because of potential side effects ribavirin should be reserved for high risk groups (Table 1) who deteriorate despite optimal supportive care. An initial trial of aggressive respiratory treatment is warranted (oxygen, hydration, bronchodilators, aspiration of secretions, etc) under very close observation and for a brief period of time (less than 6 hours). Evidence of CO<sub>2</sub> retention and/or clinical deterioration should prompt the initiation of ribavirin.

The use of ribavirin will remain controversial until studies demonstrate decreased morbidity and mortality and safety concerns are resolved. Until such time ribavirin use should be reserved for life threatening RSV infections failing to respond to optimal respiratory therapy.

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# Infections, Preterm Delivery, and Perinatal Death in Midgestation

Leila Nadra, MD  
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**Recent studies suggest that infection may be the cause rather than the result of premature rupture of membranes and premature labor. The mechanism involves damage of the amnion by bacteria.**

Preterm labor and delivery are important features of prenatal mortality and morbidity. Substantial data suggest that transcervical infection of the amniotic sac plays an etiologic role in as many as 20% of such cases.<sup>1-3</sup> Premature

rupture of placental membranes and cloudy amniotic fluid, often with a foul odor, are signs of amniotic sac infection. The placentas in such cases display chorioamnionitis and funisitis. The fetuses and neonates with this complication have pneumonia and septicemia. Less commonly, inflammatory lesions are found in meninges, skin, mucosal surfaces and deep viscera.<sup>4</sup>

The purpose of the present study is to examine the role of amniotic sac infection in fetal and neonatal death in midgestation by reviewing the autopsy files of Women and Infants Hospital during the past decade and to record the causative bacteria in these cases.

## Materials and Methods

The autopsy files at Women and Infants Hospital were searched for cases of fetuses and neonates with positive bacterial cultures during the ten year period from 1980 through 1989. Lung cultures were routinely taken by swab of the left lung and blood cultures from the right atrium. Other sites occasionally cultured included

the liver, peritoneum, pleura, pericardium, spinal fluid, brain, spleen and kidney. Aerobic and anaerobic bacteria were identified and classified according to standard bacteriologic techniques.<sup>5</sup>

Cases with negative autopsy cultures were included in the series if at least two of the following three criteria were present: 1) placental inflammation, eg, chorioamnionitis; 2) clinical or histologic evidence of bacterial infection, eg, positive cultures during life with either clinical signs of infection or inflammation of postmortem tissues such as pneumonia or meningitis; 3) clinical evidence of maternal infection including fever  $>38^{\circ}\text{C}$  and or leukocytosis  $>16,000$  WBC/mm.<sup>3</sup>

Chorioamnionitis was defined as neutrophilic infiltrates of the amnion and chorion; funisitis was defined as neutrophilic infiltrates of the umbilical cord or its ves-

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**ABBREVIATIONS USED:**  
DES: diethylstilbesterol  
WBC: white blood cell

sels; villitis was defined as neutrophilic infiltrates of the placental villi; pneumonia was defined as neutrophilic infiltrates or exudates in the parenchyma of the lung; gastrointestinal inflammation was defined as neutrophilic infiltrates or exudates in the mucus or mucosa of the GI tract.

Data also included the total number of births, fetal and neonatal deaths, and autopsies as well as similar data for fetuses and neonates born at midgestation at this hospital throughout the decade of the 1980s.

The study was limited to fetuses and neonates with a gestational age of 18-28 weeks (mid-gestation) as estimated by dates or by birthweights and measurements. Of the liveborns, only those who died during the first week of life were included so that most nosocomial infections were excluded. In each case, we reviewed the clinical information regarding previous maternal obstetric history, the gestation, and mode of delivery. Histologic reports of placentas and autopsies were also reviewed.

## Results

During the decade beginning in January 1980 through December 1989, a total of 77,674 deliveries took place at Women and Infants Hospital. There were 1,370 perinatal deaths, of which 643 were stillborn and 727 were neonatal deaths. Of the perinatal deaths, 829 occurred between 18 and 28 weeks gestation; 344 of these were stillborn and 485 were neonatal deaths. A total of 1,119 autopsies were performed here on fetuses and neonates of all gestational ages during the decade. Gestational ages were not always recorded or were considered estimates in some cases. By our best estimation, 663 (59.2%) of these autopsies were on fetuses and neonates delivered in midgesta-

tion, between 18 and 28 weeks of gestation. Of these, 133 (20.1%) were associated with midgestational bacterial infection. These cases represent 11.9% of all perinatal autopsies at this hospital.

Among the 133 cases which comprise the study group, 126 had positive cultures taken at the time of autopsy examination. The other seven had negative cultures at autopsy but had chorioamnionitis and/or funisitis or pneumonia along with either positive premortem cultures (neonatal and placental) or evidence of maternal infection.

**20.1% of autopsies (of mid-gestational fetuses and neonates) were associated with bacterial infection.**

Of the 45 stillborn fetuses, 29 were males and 16 were females. By contrast, among the liveborn neonates who died with evidence of infection before the end of the first week of life, 40 were males and 48 were females. The preponderance of males among the stillborns is statistically significant by Chi square analysis ( $p = 0.001$ ).

The liveborns survived from 2 minutes to 7 days. Birth weights ranged from 225 g to 1500 g (mean birth weight 579 g). Gestational ages, as calculated by dates from the last menstrual period ranged from 19-28 weeks (mean gestational age 24 weeks).

The types of bacteria isolated are listed in order of frequency in Table 1. Coagulase negative staphylococcus, group B streptococcus, and *Streptococcus viridans* were the most numerous isolates. These three gram-positive organisms accounted for 47.3% of the isolates.

In 81 of 133 cases (61%), pneumonia was identified in postmor-

tem examination of the lungs. Neutrophilic exudates were found in the stomach in 14 cases (10.5%) and enteritis or necrotizing enterocolitis was noted in 3 cases (2.2%). Meningitis was documented in 2 cases and peritonitis in one case. In 44 cases (33%), inflammation was absent in the tissues, that is, no histologic evidence of infection was found in the fetal or neonatal tissues although cultures were positive and placental inflammation was present.

Placental lesions included acute chorioamnionitis in 120 cases (90.2%), funisitis in 87 cases (65.4%), and villitis in 9 cases (6.8%). In only 5 cases were no signs of placental inflammation found. In 4 of these 5, pneumonia was found at autopsy and in the remaining case, tracheal ulcers with bacterial colonies were found.

Clinical data included maternal ages ranging from 17 to 42 years (mean maternal age 26.3 years). Spontaneous rupture of the membranes and/or vaginal bleeding occurred in 106 of 133 cases (79.7%) with intervals preceding delivery of 3 hours to 4 weeks. Maternal infection was documented in 41 cases (30.8%). Nineteen mothers (14.3%) had a history of incompetent uterine cervix. Two of these 19 had a previous cone biopsy and 3 had been exposed to diethylstilbesterol (DES) in utero. Similar exposure to DES in utero but without evidence of cervical incompetence was recorded in an additional 2 cases. Diabetes mellitus was diagnosed in a single case. Of the mothers, 94 were multiparas, 31 were primiparas, and in 8 cases the previous obstetric history was not available. Among the multiparas, a total of 225 pregnancies yielded only 93 living children (41%). Maternal data are summarized in Table 2.

Table 1. Organisms Isolated from Perinatal Autopsies. Cases With Clinical Pathologic Sepsis

Organisms	Total	Pure Culture	Mixed Culture
Coagulase negative staphylococcus	26	13	13
Group B streptococcus	24	17	7
Streptococcus viridans	13	6	7
Bacteroides species	13	6	7
Escherichia coli	11	5	6
Diphtheroids	9	—	9
Peptostreptococcus	8	3	5
Enterobacter cloacae	8	5	3
Coagulase positive staphylococcus	7	2	5
Pseudomonas species	7	3	4
Enterococcus species	7	1	6
Fusobacterium species	7	2	5
Klebsiella pneumoniae	6	1	5
Lactobacillus species	4	2	2
Haemophilus influenzae	4	4	—
Candida albicans	3	1	2
Corynebacterium species	3	1	2
Streptococcus, microaerophilic species	2	1	1
Clostridium perfringens	2	1	1
Gardnerella vaginalis	2	1	1
Citrobacter diversus	1	1	—
Serratia marcescens	1	—	1
Proteus mirabilis	1	—	1
Eikenella corrodens	1	—	1
Herella	1	—	1
Torulopsis glabrata	1	1	—
Haemophilus parainfluenza	1	1	—
Listeria monocytogenes	1	1	—

## Discussion

About half of the placentas from babies with birthweights less than 1000 grams have chorioamnionitis whereas only one in ten of those from full-term babies will show signs of infection.<sup>6</sup> Recent studies suggest that infection may be the cause rather than the result of premature rupture of membranes and premature labor.<sup>7, 8</sup> The mechanism involves damage of the amnion by bacteria. Prostaglandins are produced by interaction of bacteria, host leukocytes, decidua, and amnion epithelium. This is thought to result in uterine contractions.<sup>8, 9</sup> The combination of attenuated membranes and increased intrauterine pressure causes rupture and progression of labor.

Bacterial infections of the amniotic sac seem to occur fre-

quently in pregnancies of women with previously poor obstetric outcome.<sup>10, 11</sup> This was a prominent feature in this study with only 92 living children among the 225 pregnancies in the multigravida group. The repeated fetal and neonatal losses are not all necessarily due to amniotic sac infections but it is likely that in many cases this is so. In our series 14.3% of the mothers had cervical incompetence, a condition known to be associated with excessive amniotic sac infections.

Microorganisms most often isolated were: coagulase negative staphylococcus — 19.5%, group B streptococcus — 18%, *Streptococcus viridans* — 9.7%. These 3 gram-positive organisms accounted for almost half of the cases in this study. Gram-negative organisms in aggregate ac-

counted for 41%; bacteroides species — 9.7%, and *Escherichia coli* — 8.2% were the most common gram-negative organisms isolated (Table 1).

In studies of perinatal sepsis in the past 3 decades group B Streptococcus has received the most attention.<sup>4, 11-14</sup> In our study, group B streptococcus was the second most frequently isolated organism. This organism is part of the normal female genital flora and can be found in vaginas of 10% of pregnant women and 25-35% of parturient women. Rectal cultures are often positive and the urinary tract may also be a source of the organism.<sup>15</sup> Although the majority of infected pregnant females have normal healthy infants, 1%-2% result in either stillbirths or infants with neonatal disease.<sup>14</sup> In a previous review of autopsy material at Women and Infants Hospital, 32 fetuses and neonates had infections with group B streptococcus and 11 (34%) of these were of midgestational age.<sup>11</sup>

**Three gram-positive organisms (coagulase-negative staphylococcus, group B streptococcus and Streptococcus viridans) accounted for 47.3% of the isolates.**

Coagulase negative staphylococcus is now recognized as a significant pathogen in neonates, more numerous than Gram-negative organisms in some recent studies.<sup>16-18</sup> It was the most common organism isolated in this study. Recently, Freeman *et al*, have claimed a role for intravenous lipid infusions in the emergence of this organism as a serious pathogen.<sup>18</sup> In our study, many of the stillborn fetuses had this organism isolated and none had received intravenous alimen-

tation with lipids.

*Streptococcus viridans* in the past has been regarded as a relatively innocuous organism capable only of producing indolent infections such as subacute bacterial endocarditis. Indeed, growth of any alpha-hemolytic streptococcus in premature infants was regarded as a contaminant.<sup>19</sup> In the past two decades *Streptococcus viridans* has become increasingly recognized as a source of serious infection in neonates.<sup>13, 20</sup>

In this study *Streptococcus viridans* was found in 13 cases; in 6 cases as a pure organism and in 7 cases in a mixed culture. It seems to have a significant role in the pathogenesis of the mid-trimester abortions either alone or in combination with other bacteria.<sup>21</sup>

Bacteroides species occurred with frequency equal to *Streptococcus viridans*. These anaerobic gram-negative organisms are part of the indigenous vaginal microflora in healthy women, together with other anaerobes such as peptostreptococci and bifidobacteria. All anaerobes together accounted for 22% of the cases. According to Pankuch *et al*, the most frequent high-virulence isolates in the amniotic fluid infections are bacteroides species.<sup>22</sup>

In our study, infections with *E. coli* were far less numerous than infections with any one of several different species of gram-positive organisms. Fungal (yeast) infections were found in 4 cases *Candida albicans* was cultured in 3 and *Torulopsis glabrata* in 1 case. *Listeria monocytogenes* was demonstrated in only one case.

Males were significantly more numerous than the females among the stillborn fetuses with infection. This isolated observation is puzzling. No recognized cause is known for a gender difference in fetal deaths due to infection. In the liveborn group and

Table 2. Perinatal Infections, Maternal Data

Age range	17-42 years	
Mean age	26.3 years	
Spontaneous rupture of membranes and/or vaginal bleeding	106/133	79.7%
Maternal fever > 38° C or WBC > 16,000	41/133	30.8%
Cervical incompetence	19/133	14.3%
Previous cone biopsy	2/133	1.5%
Exposure to DES in utero	5/133	3.7%
Primipara	31/125	24.8%
Multipara	94/125	75.2%
Total pregnancies	225	
Living children	92	

in the study groups together, the females and males were present in approximately equal numbers.

Pneumonia was found in 81 of 133 cases (61%). The involvement of the lungs is recognized as one of the more important and common manifestations of neonatal sepsis. It is frequently associated with exudate in the gastrointestinal tract, presumably as a result of swallowing infected amniotic fluid. Gastrointestinal leukocytic exudates occurred in 14 of our 133 cases (10.5%). Meningitis may occur in 25-30% of cases of neonatal sepsis but in our study this was documented in only 2 cases. This low incidence may be related to the limits of our study group, ie, fetuses and neonates in midgestation and postnatal ages less than 7 days. Other signs of sepsis in this series included enteritis or necrotizing enterocolitis in 3 cases and peritonitis in 1 case.

No histologic features of infection were found in lungs or other organs in 44 of our 133 cases (33%). These cases are nevertheless included because infection played a role in their premature delivery and demise. Evidence for infection was found in the positive postmortem cultures and in the clinical evidence of maternal infection. Chorioamnionitis was also found in each of these 44 cases.

## Summary

Amniotic fluid infection results in considerable pregnancy wastage in the second and early third trimesters.<sup>3, 8</sup> In our study of 1119 perinatal autopsies amniotic sac infection was associated with death in 133 fetuses and neonates in midgestation. These cases accounted for almost 12% of all perinatal autopsies and for 20% of all perinatal autopsies in midgestation at Women and Infants Hospital during the past decade. Gram-positive organisms, especially coagulase negative staphylococcus, group B streptococcus and *Streptococcus viridans*, were the most common pathogens isolated.

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Am Fam Phys 1987;36:133-140

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#### Brief Summary.

Consult the package literature for prescribing information. Indication: Lower respiratory infections, including pneumonia, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes* (group A  $\beta$ -hemolytic streptococci).

Contraindication: Known allergy to cephalosporins.

Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

#### Precautions:

- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of non-susceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

#### Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon.

Those reported include:

- Hypersensitivity reactions have been reported in about 1.5% of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions have been reported with the use of Ceclor. These are characterized by findings of erythema multiforme, rashes, and other skin manifestations accompanied by arthritis/arthralgia, with or without fever, and differ from classic serum sickness in that there is infrequently associated lymphadenopathy and proteinuria, no circulating immune complexes, and no evidence to date of sequelae of the reaction. While further investigation is ongoing, serum-sickness-like reactions appear to be due to hypersensitivity and more often occur during or following a second (or subsequent) course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults with an overall occurrence ranging from 1 in 200 (0.5%) in one focused trial to 2 in 8,346 (0.024%) in overall clinical trials (with an incidence in children in clinical trials of 0.055%) to 1 in 38,000 (0.003%) in spontaneous event reports. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy; occasionally these reactions have resulted in hospitalization, usually of short duration (median hospitalization = two to three days, based on postmarketing surveillance studies). In those requiring hospitalization, the symptoms have ranged from mild to severe at the time of admission with more of the severe reactions occurring in children. Antihistamines and glucocorticoids appear to enhance resolution of the signs and symptoms. No serious sequelae have been reported.
- Stevens-Johnson syndrome, toxic epidermal necrolysis,

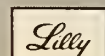
and anaphylaxis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy.

- Gastrointestinal (mostly diarrhea): 2.5%
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertension, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1% and, rarely, thrombocytopenia and reversible interstitial nephritis.

Abnormalities in laboratory results of uncertain etiology

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- Transient lymphocytosis, leukopenia, and, rarely, hemolytic anemia and reversible neutropenia.
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# Acute Bacterial Meningitis in Rhode Island: A Survey of the Years 1976 to 1985

Stanley M. Aronson, MD, MPH  
Barbara A. DeBuono, MD, MPH  
Jay S. Buechner, PhD

***There were 667 recorded cases of bacterial meningitis in the hospitals of Rhode Island during the ten year interval . . . an average annual incidence rate of 6.9 cases per 100,000 population.***

The incidence of bacterial meningitis is rare enough to give the appearance of random distribution. The average physician may see but a handful of cases in a lifetime of clinical practice. Only after access to extensive popu-

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lation-based data, covering extended time intervals, can one then discern secular trends, changes in the frequencies of certain organisms, epidemic cycles of some organisms but not others, patterns of selective vulnerability and the significant influence of *individual* risk factors (such as low birth weight, fusion-defect anomalies of the central nervous system, head injury, immune deficiency, aging, antineoplastic therapies and diabetes mellitus) and *collective* risk factors (such as imprisonment, migration, socio-economic status and season of the year) upon the incidence rates of acute central nervous system infections.

This brief report provides demographic and bacteriologic summaries of a ten-year retrospective survey of acute bacterial meningitis in Rhode Island covering the years 1976 through 1985.

## Methods

The discharge data from the hospitals of Rhode Island, for the years 1976 to 1985, were reviewed and all cases of bacterial men-

ingitis were extracted. For inclusion in this retrospective survey, the following criteria were required: A clinical diagnosis of acute meningitis and at least one lumbar puncture yielding species-identifiable bacteria. Cases of meningitis caused by mycobacteria, fungi or viruses were excluded.

## Results

By the criteria mentioned above, 667 cases of acute bacterial meningitis were collected, with an average annual incidence rate of 6.9 cases per 100,000 population (Table 1). When age of the patient is then considered, the rate is shown to be highest in the neonatal interval (98.7 per 100,000); it drops to a low of 2.2 per 100,000 in late adolescence and then rises to 9.4 per 100,000 in patients beyond the age of 65 years. There were slightly more affected males (341 cases) than females (326 cases) in this survey.

## ABBREVIATIONS USED:

CFR: case fatality rate

Mgemia: meningococcemia

There were 69 immediate deaths in this series (crude case fatality rate (CFR) of 10.3%). The CFR, however, was substantially higher in those meningitis patients older than 65 years (Table 1) accounting, during this decade, for 67% of all meningitis deaths in the state. The overall crude CFR was higher in females (12%) than in males (8.8%), but most of the cases of meningitis in the very elderly were in females.

Table 2 lists the dominant organisms recovered in this series of 667 cases. *Hemophilus influenzae* was the causative agent in 247 cases (37%), *Neisseria meningitidis* (meningococcus) in 117 cases (18%), *Streptococcus pneumoniae* (pneumococcus) in 124 cases (19%), and the various coliform organisms in 51 cases (8%). Miscellaneous bacteria accounted for another 120 cases (18%).

When the variables of age and sex are now related to the four most frequently encountered organisms (Table 3), the following becomes apparent: Below the age of 16 years, the number of affected males were 246 and the number of females, 188. There were significantly more young males with *H. influenzae* meningitis (142 cases) than females (86 cases). Beyond the age of 65 years, bacterial meningitis was predominantly female (25 cases in males and 59 cases in females).

The great majority of patients with *H. influenzae* meningitis, in this series, were younger than 5 years (228 of 247 cases, 92%). Only 6 of these cases (2%) were in patients older than 65 years. In contrast, 55% of the cases of meningococcal meningitis and 29% of cases of pneumococcal meningitis were five years of age or younger.

Between the ages of 16 and 65

Table 1. Bacterial Meningitis in the State of Rhode Island 1976-1985

Age	Cases	Deaths	CFR*	Pop.†	I.R./100K/Yr•
< 1	232	10	4.3	23,500	98.7
1-5	168	1	0.6	93,100	18.1
6-15	34	6	17.6	152,400	2.2
16-65	149	6	4.0	610,900	2.4
66 +	84	46	54.8	89,800	9.4
ALL	667	69	10.3	969,700	6.9

\* case fatality rate (%).

† population of Rhode Island (1980).

• incidence rate per 100,000 population per year.

Table 2. Bacterial Meningitis in the State of Rhode Island 1976-1985

Organism	Males	CFR[%]*	Females	CFR[%]
	No.		No.	
H. influenzae	151	2.0	96	2.0
N. mening.	52	2.0	65	7.7
S. pneumoniae	55	20.0	69	17.4
Coliforms	21	28.6	30	23.3
Other bact.	62	14.5	66	19.7
TOTAL	341	8.8%	326	12.0%

\*case fatality rate

Table 3. Bacterial Meningitis in the State of Rhode Island 1976-1985

Age yrs	H. infl.		N. mening.		S. pneum.		Coliforms		Other	
	M	F	M	F	M	F	M	F	M	F
< 1	65	39	18	23	14	12	13	11	18	19
1-5	75	42	14	9	2	8	2	3	8	5
6-15	2	5	4	5	5	3	0	3	6	1
16-65	8	5	15	23	25	24	4	5	18	22
66+	1	5	1	5	9	22	2	8	12	19
ALL	151	96	52	65	55	69	21	30	62	66

Table 4. Bacterial Meningitis in the State of Rhode Island 1976-1985. Meningococcal Meningitis (117 cases)

Age	No. Cases	No. Mgemia*	CFR†	
			Mgemia (+)	Mgemia (-)
< 1	41	7	100.0	5.9
1-5	23	2	50.0	4.8
6-15	9	2	50.0	12.5
16-65	38	2	0.0	0.0
66+	6	0	0.0	50.0

\*meningococcemia

†case fatality rate (%).

Table 5. Bacterial Meningitis in the State of Rhode Island, 1976-1985. Coliform Meningitis, Associated Disorders

0-5 Yrs Old (N = 29)	
Cranial fusion defects: (6/29)	= 20.7%
Prematurity, low birth wgt.: (12/29)	= 41.4%
Perinatal difficulties: (11/29)	= 37.9%
Otitis media: (2/29)	= 6.9%
Necrotizing enterocolitis: (3/29)	= 10.3%
Bacteremia: (7/29)	= 24.1%
6-65 Yrs Old (N = 12)	
Major body trauma: (4/12)	= 33.3%
Intracranial neoplasm: (3/12)	= 25.0%
Bacteremia or pyuria: (5/12)	= 41.7%
66+ Yrs Old (N = 10)	
Bacteremia: (5/10)	= 50.0%
Diabetes mellitus: (4/10)	= 40.0%
Trauma, rhinorrhea: (3/10)	= 30.0%
Carcinomatosis: (2/10)	= 20.0%

Table 6. Frequency of Bacterial Organisms in Acute Meningitis

Organism	Series A	Series B	Series C	Series D
H. influenzae	57 (35.2)*	458 (34.8)	1885 (43.1)	247 (37.1)
N. mening.	32 (19.8)	396 (30.1)	1384 (31.7)	117 (17.5)
S. pneumo.	36 (22.2)	178 (13.5)	456 (10.4)	124 (18.6)
Other	37 (22.8)	284 (21.6)	645 (14.8)	179 (26.8)
Total	162 (100)	1315 (100)	4370 (100)	667 (100)

Series A: Olmsted County, Minnesota 1935-70 (2).

Series B: Chicago, Illinois, 1954-76 (3).

Series C: Centers for Disease Control, U.S.A., 1978 (4).

Series D: Present survey, Rhode Island, 1976-85.

\* number of cases and percent in parentheses.

years, the most frequently encountered organisms were *S. pneumoniae* (57 cases) and *N. meningitidis* (47 cases).

Of the 117 cases of meningitis caused by the *N. meningitidis*, 13 had positive blood cultures (meningococemia) and showed clinical evidence of disseminated infection such as cutaneous and/or conjunctival petechiae (Table 4). The CFR was substantially higher when the infection was disseminated. There were 41 cases of *N. meningitidis* infection in children below age one year. In the absence of meningococemia, there were 34 cases with two deaths (CFR, 6%); with meningococemia, all seven infants died.

In this series, there were 51 cases of meningitis ascribed to coliform organisms (Table 5). Of the 29 cases in patients 5 years or younger, 12 were described as premature at birth, 11 had some sort of perinatal difficulty which required intervention, 6 had cranial fusion defects such as meningocele, and two had prior or concurrent bacterial otitis media.

On the 12 cases of coliform meningitis between ages 6 and 65 years, four had experienced major body injury such as an automobile accident within a month of the initiation of meningitis. Three others had an intracranial neoplasm.

Of the ten cases of coliform meningitis who were 66 years or

older, three had suffered recent body injury (two with rhinorrhea presumed to represent cerebrospinal fluid leakage). Four of the ten were diabetic and two further patients had disseminated cancer. Thus, nine of the ten elderly patients with coliform meningitis were ill or physiologically impaired prior to the development of meningitis.

## Discussion

The annual incidence rate of 6.9 per 100,000 likely represents the lower limits of meningitis frequency in the Rhode Island population since the following categories of meningitis cases eluded this survey: those treated at home; those treated in hospitals outside of Rhode Island; those hospital cases where no lumbar puncture had been performed or where the laboratory had failed to recover an organism; those cases treated as disseminated infection without specific identification of leptomenigeal involvement; those in which the diagnosis was never considered and a lumbar puncture had not been performed. Other meningitis surveillance programs have nevertheless suggested rates which are quite close to the suggested estimate for Rhode Island. In Los Angeles County, for example, the 1975 rate was 7.3 per 100,000.<sup>1</sup>

When various retrospective series are compared (Table 6), moderate differences in the frequency of causative agents emerge.<sup>2,4</sup> *H. influenzae* however remains the dominant organism in all series, but in some *N. meningitidis* is more common than *S. pneumoniae* and in others the relationship is reversed. These differences may reflect different denominator populations: some data were derived exclusively from municipal hospitals for the indigent<sup>1,3</sup> while others represent data from a broader socioeco-

conomic source.<sup>2</sup> Furthermore, there are notable differences in age profile, in the regions surveyed, in the relative frequencies of ethnic groups in such regions and in the years surveyed. Fraser and others have shown that the risk of certain forms of bacterial meningitis, particularly pneumococcal, may be related to differences in income, exposures to head injury, rates of chronic alcoholism and even to levels of education.<sup>5-9</sup> In a careful survey of meningitis in Charleston County, South Carolina, the risk of pneumococcal meningitis was demonstrated to be more than five-fold greater in black children, particularly those with sickle-cell disease.<sup>10</sup> The annual rate of *H. influenzae* meningitis in native Alaskan children was ten times greater than the rates recorded for white children.<sup>6</sup>

The role of preceding disease, particularly immune deficiency, as a potent risk factor for meningitis is vividly illustrated in the eleven cases of cryptococcal meningitis occurring in the Rhode Island hospitals during this ten year survey interval. These cases, of fungal etiology, while not included in the 667 cases reviewed above are nevertheless instructive in that ten of the eleven had some compromising factor before the development of meningitis (eg, AIDS, leukemia, aplastic anemia, agranulocytosis).

### Summary

There were 667 recorded cases of bacterial meningitis in the hospitals of Rhode Island during the ten year interval of 1976 to 1985 yielding an average annual incidence rate of 6.9 cases per 100,000 population, and a case fatality rate of 10.3%. These rates are similar to those generated in other retrospective surveys in the United States.

This survey corroborates the well-established observation that bacterial meningitis is largely a disease of early childhood. But these data also suggest that meningitis in the very elderly is more common than had previously been assumed. Many of the elderly cases in this series, particularly those caused by the coliform organisms, followed shortly after body trauma or appeared in individuals burdened by disseminated cancer or diabetes mellitus.

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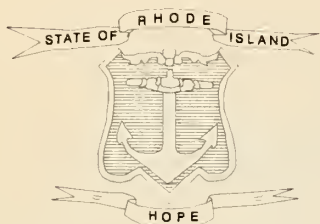
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# HEALTH BY NUMBERS

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Department of Health  
H. Denman Scott, MD, MPH  
Director of Health

## Measles 1990

Thirty-two cases of measles were reported to the Rhode Island Department of Health during the first ten months of 1990. The first reported case had rash onset of 1/26/90 and the last reported case had rash onset occurring 10/28/90. Of those cases reported fourteen (44%) were epidemiologically linked to another case and twenty-one (66%) were serologically confirmed.

Twelve (38%) measles cases occurred in children under the age of 5, including seven cases in children less than 16 months of age. Eleven (34%) cases were ages 5-19. Nine cases (28%) were 20 years old or older, including six born before 1957.

Ten (31%) patients had been vac-

cinated, including three who were vaccinated after exposure. Of the twenty-two unvaccinated patients, nine (41%) should have received vaccine according to routine indications and are therefore considered preventable cases (Table 1). Of those for whom vaccine was not recommended, seven (32%) were < 16 months of age and six (27%) were born before 1957.

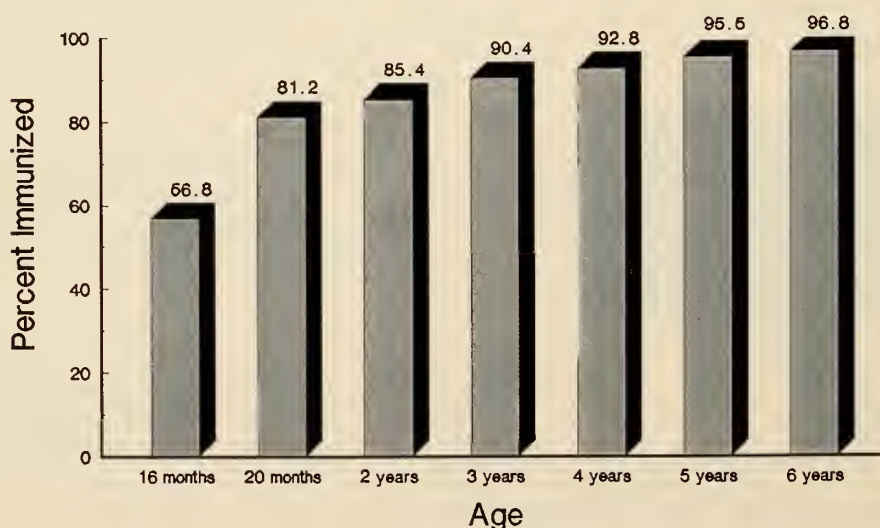
At least seven (22%) persons acquired measles through exposure in two hospital emergency rooms. This group includes four persons under the age of 19, none of whom were known to be immunized.

Control efforts included five clinics which were held to vaccinate at-

tendees at two elementary schools, one K-12 school, one post-secondary school, and one daycare center in which cases occurred. Over 1400 doses of measles-mumps-rubella (MMR) vaccine were administered at these clinics at a cost of over \$20,600. In addition, over 500 doses of measles vaccine were distributed to immunize employees and contacts at four hospitals.

In December 1989 the Rhode Island Department of Health issued new measles prevention recommendations. It is recommended that Rhode Island children receive two doses of MMR vaccine. The first dose should be given at 15 months of age and the second dose at or before en-

Figure 1: 1989 Retrospective Survey of Kindergarten Students' MMR Immunization Rates.



Submitted by the Office of Disease Control, Epidemiology and Communicable Diseases Division, Barbara A. DeBuono, MD MPH, Medical Director, Thomas T. Gilbert, MD MPH, and Kim Salisbury-Keith, MBA. *Health by Numbers* is edited by Jay S. Buechner, PhD, and William J. Waters, Jr., PhD.

try to sixth grade. School regulations currently required only one dose on or after the age of 15 months for new enterers less than 7 years of age.

A school immunization survey done in the fall of 1989 showed that, statewide, 95% of entering kindergarten students, 95% of entering transfer students, and 98% of seventh graders were fully immunized for all required antigens. In general, survey results for individual cities and towns were comparable to statewide rates. However, in the Providence public school system, only 88% of new enterers were fully immunized while 95% of seventh graders were fully immunized. Providence data reflect the

inner city minority character of the city schools and suggest that inner city, minority and immigrant preschool children may be poorly immunized.

In addition, a random sample of students entering kindergarten in the fall of 1989 were selected for a study of immunization coverage among preschoolers. Their immunization records were reviewed to determine immunization status at selected ages. Statewide, 85.4% had received MMR by age two and 96.8% by the age of six (Figure 1).

Age appropriate vaccination along with prompt reporting of all suspected measles cases will aid in con-

trolling any future outbreaks. To control the nosocomial spread of measles it is important that all hospital emergency rooms and medical providers promptly recognize and isolate all suspect rash illnesses.

Table 1: Distribution of Measles Cases by Age, Vaccination Status and Preventability

<u>Age</u>	<u>Cases</u>	<u>Vaccinated</u>	<u>Preventable*</u>
< 16 mo	7	0	0
16 mo – 4 yrs	5	3	2
5 – 9 yrs	11	7	4
20 – 33 yrs	3	0	3
> 33 yrs	6	0	0
Total	32	10	9

\*Should have received vaccine according to routine indications .

R H O D E  
STATE OF ISLAND

# Monthly Vital Statistics Report

## Provisional Occurrence Data From the Division of Vital Records

H. Denman Scott, MD, MPH  
Director of Health

Roberta A. Chevoya  
State Registrar

Vital Events	Reporting Period	12 Months Ending with September 1990	
	September 1990 Number	Number	Rates
Live Births	1,543	15,983	15.0*
Deaths	722	9,797	9.8*
Infant deaths	(7)	(140)	8.8†
Neonatal deaths	(5)	(108)	6.8†
Marriages	1,230	8,239	8.3*
Divorces	249	3,842	3.8*
Induced Terminations	631	7,854	491.4†
Spontaneous Fetal Deaths	117	1,125	70.4†
Under 20 weeks' gestation	(112)	(1,039)	65.0†
20 + weeks' gestation	(5)	(85)	5.3†

\*Rates per 1,000 estimated population.

†Rates per 1,000 live births.

Underlying Cause of Death Category	Reporting Period	12 Months Ending with June 1990		
	June 1990 Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	268	3,466	347.3	5,028.5
Malignant Neoplasms	196	2,409	241.4	6,681.5
Cerebrovascular Diseases	49	599	60.0	704.5
Injuries (Accident, Suicide, Homicide)	39	454	45.5	10,072.5
COPD	33	366	36.7	393.0

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 current estimated population of 998,000.

(c) Years of Potential Life Lost (YPLL)

NOTE: Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

# THE RHODE ISLAND MEDICAL JOURNAL

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Issued Monthly under the direction of the Publication Committee

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## THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

### *Fifty Years Ago (January, 1941)*

The lead article is an essay on obstructed labor by Dr George W. Waterman. The author defines his subject as follows: "Labor is spoken of as being obstructed when progress of the head through the pelvis has come to a standstill and when further progress by means of the natural forces seems impossible, or better perhaps, improbable." He states further, "... with time and moulding and adaptation of the fetal presenting part, a favorable outcome will sometimes occur in spite of marked pelvic abnormality or cephalopelvic disproportion."

"If one is properly prepared, knows his landmarks, makes a good diagnosis of what is happening and of the type of mechanism with which he has to deal, then his operation is by just so much simplified. One makes an accurate application and knowing much about the mechanism required he with great gentleness and the minimum of force guides the head through the most favorable path."

The author concludes: "As an aid in diagnosis of size and shape of the pelvis the stereoscopic X-ray can be of great value and is so proving to those who are prop-

erly familiar with it. The decision to perform Caesarian section on X-ray findings alone is, however, bad, for the X-ray picture gives us no idea of the adaptability of the particular fetal head to the particular pelvis. We still have babies delivered normally through pelves which look very treacherous before a proper trial of labor proves them not to be. Unless the indication is absolute, therefore, a trial is in order. To conduct this trial we come back to first principles, a knowledge of how the head engages and how it finds its way through the difficult pelvis. Only by constant and careful observation hour by hour, with experience of many examinations during labor, is this knowledge obtained, but once one opens his mind and gives time and thought to it there is no more fascinating or worthwhile study in medicine or surgery."

Dr Charles Potter writes an article entitled, Manual Removal of the Placenta. The author observes: "It has been repeatedly stated that removal of the placenta manually is an extremely dangerous procedure." He then provides mortality rates in various previously published surveys, varying from 8 to over 50 percent.

During the twelve preceding years at Providence Lying-In Hospital, he reports, there have been 31,831 deliveries of viable infants and 158 instances of manual removal of the placenta (0.48 percent). In this series there were two maternal deaths, with a gross mortality rate of 1.27%.

The author concludes: "1. The incidence of manual removal of the placenta at the Providence Lying-In Hospital during the past twelve years was one in 208 cases. 2. Certain obstetrical complications in pregnancy seem to predispose to third stage difficulty. 3. Patients with long exhausting labors or difficult operative deliveries often require manual removal of the placenta. 4. The indications for manual removal were hemorrhage, retention, and the patient's condition, with hemorrhage the most common. 5. The gross morbidity rate was 32.3%, over six times the hospital average. Failure to completely remove the placenta and packing increased the morbidity rate to 83.3% and 52.2% respectively. 6. The gross maternal death rate was 1.27% and the corrected rate 0.63%. 7. A policy of noninterference except where clearly indicated will reduce the necessity for manual removal."

Dr Adolph W. Eckstein discusses the Tragedies and Calamities of Surgery, quoting extensively from the published clinical experiences of James Paget. The author then describes the various calamities which may arise during the course of contemporary surgical intervention. He concludes: "To avoid these calamities and tragedies we must scrupulously watch ourselves; for in proportion as our patients are helpless, the more it rests upon our consciences to stand in their place and help them. We must govern ourselves in surgery by such rules that we may be able to escape the regrets of such calamities. Consideration of the liability of these calamities should be an incentive to take careful case histories, make good physical examinations, to overcome all avoidable ignorance, and to practice constant discipline in watchfulness, that one may overlook nothing that can contribute to a patient's welfare."

Dr Francis E. Hanley writes on Local Refrigeration and Hibernation in the Treatment of Cancer. As to results of such treatment, he states that no definite conclusions can as yet be reached. He concludes: "I would state that the small hospital is no place to attempt to answer the experimental questions involved; but I do believe that hibernation treatment of extreme hopeless cases for the short period of twenty-four hours for palliative purposes only is possible and could be successfully instituted."

The lead editorial, entitled, The Problem of the Aged, states the paradox that this problem with the impaired aged has been "... created in a large measure by public health activities in the field of preventive medicine and that the medical profession in their advances of the past twenty years have contributed in a large meas-

ure to the problem." The editorial observes that older people, particularly with senile dementia, are increasingly occupying the beds of inpatient facilities with increasing costs to the taxpayers. The editorial urges the reader "... before signing certificates of mental disorder ... the local practitioners would thoroughly investigate the possibilities of looking after the patient in the community." (*Editorial Note: This January, 1940, editorial is worth reading in its entirety. Were it to be published today, fifty years later, it would be regarded as eminently relevant and perceptive. The problem still remains unanswered.*)

The minutes of the Providence Medical Association notes the need for physicians to fill out the AMA questionnaire for the Induction Boards (*Editorial Note: This, 11 months before the attack on Pearl Harbor.*)

### ***Twenty-Five Years Ago (January, 1966)***

The principal article represents a talk given by Dr John H. Knowles, general director of Massachusetts General Hospital, before the 33rd Annual Meeting of the Hospital Association of Rhode Island. The essay, entitled, The Changing Hospital and its Associations, discusses the future role of the general hospital in the community and in medical care. He concludes: "Medicine now is trying to get itself back into the university and to make better use of the social sciences. There will be a dialogue with political economists, political scientists, economists, demographers and social scientists. ... There is a power vacuum in the inner councils of decision-making in regard to the future of medicine in this country. There aren't many politicians who will listen to the state medical so-

ciety and the AMA much longer. Perhaps a new pattern will emerge, unless medicine steps back into its social responsibility and stops talking about who is paying whom, and whether radiologists should receive higher salaries. ... If we are not good politicians there will be someone else telling us what to do — Madison Avenue, the television set, or state and federal government. You must participate and keep voluntary local initiative alive, if you don't want to see everything go down to Washington."

The *Journal* publishes a comprehensive symposium on the medical and surgical aspects of shock, chaired by Dr Stephen J. Hoyer and with contributions by Drs J.H. Moyer, L.C. Mills, and E.D. Frank. The symposium touches upon the effects of vasopressor agents in shock, cerebral circulatory changes associated with hypotension, the effects of various pharmacologic agents on lowered blood pressure, renal aspects of shock, and the management of surgical shock through bedside monitoring.

Dr L.A. Senseman writes on the housewife's secret illness and how to recognize the female alcoholic. The author describes six years of experience at the Fuller Memorial Sanitarium in the care and management of the female alcoholic. The article provides a demographic profile of 232 such admissions.

The *Journal* prints an analysis, prepared by the Legislative Department of the AMA, describing recent federal legislation (Public Law 89-239) pertaining to heart disease, cancer and stroke. The major purposes of this law are to encourage the establishment of regional cooperative arrangements among medical schools, research institutes and hospitals for research and training in heart disease, cancer and stroke.

Dr D.E. Reid writes on the future of specialty hospitals (and lying-in hospitals, particularly). He concludes that these specialized institutions, to survive, must either merge with general hospitals or at least closely affiliate themselves with such institutions so as to have available the ambulatory, diagnostic, special care and emergency room facilities which they customarily lack.

The lead editorial debates the future of the Charles V. Chapin Hospital. Another editorial is entitled *Drugs, Doctors and Danger*, and the *Daily Press*. The writer calls to task the daily press as "...persistent offenders in encouraging that frenetic and beguiling pharmaceutical advertising and the widespread use of nearly worthless medications. . . ."

Other editorials touched upon the shortage of potable water and Project Head Start.

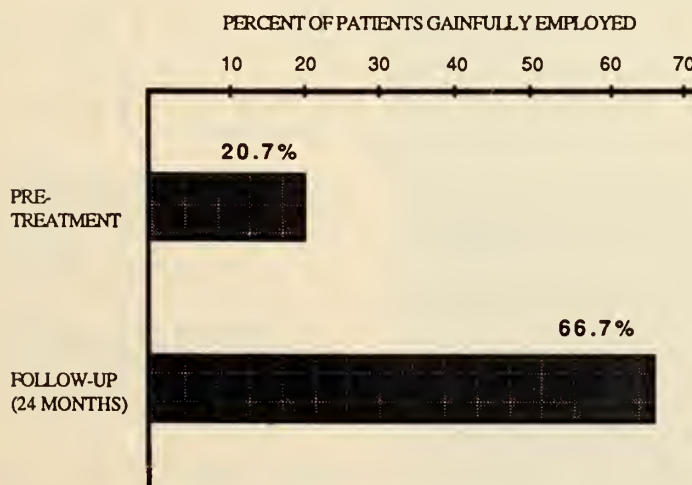
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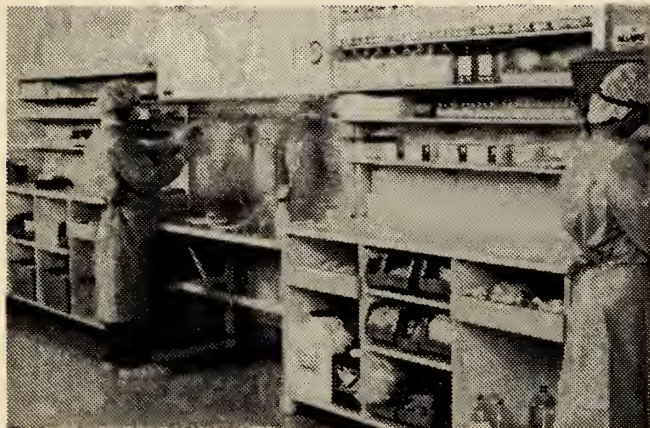
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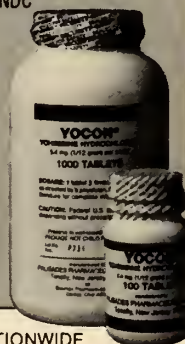
**Dosage and Administration:** Experimental dosage reported in treatment of erectile impotence.<sup>1,3,4</sup> 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.<sup>3</sup>

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**References:**

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4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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## NECROLOGY 1990

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### **Mark Rittner, MD**

Doctor Mark Rittner, an ear, nose and throat specialist who practiced in Providence until his retirement in 1984, died January 3, 1990, at the age of 95.

Doctor Rittner graduated from Tufts Medical School and served on the staffs of Massachusetts General Hospital, the Lahey Clinic and Rhode Island Hospital. He was a member of the American Medical Association, the Massachusetts Medical Society and the Rhode Island Medical Society. He was also treasurer of the American Medical Association of Vienna.

Doctor Rittner was the husband of Madeline (Seltzer) Rittner.

### **Nicola Di Palma, MD**

Doctor Nicola Di Palma, chief anesthesiologist at the Veterans Administration Medical Center for the past four years, died February 3, 1990, at the age of 65.

Doctor Di Palma was a 1948 graduate of the University of Naples Medical School. He had general practice in Providence from 1952 to 1968. From 1968 to 1985, he was on the staff of St Joseph Hospital, Roger Williams General Hospital, Rhode Island Medical Center, and the former Mercy Hospital in Woonsocket. He was chief of anesthesiology at the former Fogarty Memorial Hospital, North Smithfield, in 1985. Doctor Di Palma was a member of the Rhode Island Chapter of the American Society of Anesthesiologists and the Rhode Island Medical Society. He was a fellow of

the American College of Anesthesiologists.

Doctor Di Palma was the husband of Maria L. (Mezzadri) Di Palma.

### **Simon L. Blumen, MD**

Doctor Simon L. Blumen, a family practice physician, died March 4, 1990 at the age of 64.

Doctor Blumen graduated from medical school in Jerusalem, Israel in 1953. Doctor Blumen was made a fellow of the American Board of Family Practice in 1972. He had been a member of the Providence Medical Association and the Rhode Island Medical Society since 1959.

### **Ezra A. Sharp, MD**

Doctor Ezra A. Sharp, a practicing physician in Providence for 60 years, died March 25, 1990, at the age of 88.

Doctor Sharp received his medical degree from Johns Hopkins University School of Medicine in 1925. He began practicing in Rhode Island in 1929 and was on the staffs of the former Charles V. Chapin Hospital, Rhode Island Hospital and Miriam Hospital. He also served as physician-in-chief at Miriam Hospital.

Doctor Sharp was a fellow of the American College of Physicians, a member of the American Society of Internal Medicine, the American Physicians Fellowship, The American and Providence Medical Associations and the Rhode Island Medical Society.

### **Francis H. Chafee, MD**

Doctor Francis H. Chafee, a long-time physician in Providence, died April 24, 1990, at the age of 86.

Doctor Chafee graduated from Harvard Medical School in 1931. He practiced in Providence from 1933 to 1975. He was on the staff at Rhode Island Hospital and was founder and director of its allergy clinic from 1938 to 1965. He was a consultant in allergies at the Veterans Administration Medical Center, Butler Health Center and Miriam Hospital. Doctor Chafee served in the Division of University Health at Brown from 1935 to 1965.

He was a member of the American College of Physicians, the American Academy of Allergy (serving as vice president in 1968), the American College of Allergists, the American Medical Association, the American Federation of Clinical Research and the International Society of Allergists. Doctor Chafee was president of the Providence Medical Association in 1955, the New England Society of Allergy, and Rhode Island Society of Allergy from 1970-72. He was in the Army Medical Corps in World War II, serving in Europe for three years and attaining the rank of major.

Doctor Chafee was the husband of Jane (Spofford) Chafee.

### **Malcom A. Winkler, MD**

Doctor Malcom A. Winkler, a dermatologist, died May 7, 1990, at the age of 82.

Doctor Winkler graduated from Tufts University Medical School

in 1935 and did graduate study in New York from 1937 to 1939 at the Columbia University College of Physicians and Surgeons and the New York University School of Medicine's skin and cancer unit.

He established a dermatology practice in Providence in 1939. He served on the staffs of Rhode Island Hospital, St Joseph Hospital and Miriam Hospital, where he had been chief of staff. He served in a consulting capacity at Charles V. Chapin Hospital, the former Our Lady of Fatima Hospital, and Roger Williams General Hospital. He was a medical adviser to Governor John A. Notte.

Doctor Winkler was a diplomate of the American Board of Dermatology, a fellow of the American Academy of Dermatology, and a member of the American Association of Dermatologists, the International Congress of Dermatology and the American Medical Association. He was a charter member of the International Society of Tropical Medicine, a past president of the Rhode Island Dermatological Society, and a member of the new England Dermatological Society, the Rhode Island Medical Society (honored for 50 years of membership in 1989), the Providence Medical Society and the American Medical Writers Association.

#### **Henry J. Krawczyk, MD**

Doctor Henry J. Krawczyk, a cardiologist, died May 24, 1990, at the age of 66.

Doctor Krawczyk was a 1952 graduate of Georgetown Medical School. He was on the staff of the Veterans Administration Medical Center for many years before retiring in 1988. He also served on the staff of Miriam Hospital, St Joseph Hospital, and was a consultant at Roger Williams General Hospital and Women and Infants

Hospital. He was a member of the Rhode Island Medical Society, American Medical Association, Providence Medical Association and the Massachusetts Heart Society.

Doctor Krawczyk was the husband of F. Barbara (Hughes) Krawczyk.

#### **Max Faintych, MD**

Doctor Max Faintych, a psychiatrist, died June 2, 1990, at the age of 60.

Doctor Faintych received his medical degree from the University of Parana, Brazil, now the School of Health Sciences of the Federal University of Parana, in 1954. He was senior psychiatric physician for the Rhode Island State Hospital, now the Institute of Mental Health in Cranston. He studied at Harvard Medical School, continuing medical education, advance course in psychotherapy in 1969 and 1970. He was a psychiatric consultant for the US Selective Service (RI Boards) from 1959 to 1971, the Office of Disability Determination, and the Social Security Administration from 1960 to 1963. He was clinical psychiatrist for the Warwick Community Guidance Clinic and consultant to program counselors, RI Division of Vocational Rehabilitation. He was attending psychiatrist at Rhode Island Hospital from 1960 to 1967, Charles V. Chapin Hospital from 1960 to 1967, Butler Hospital from 1960 to 1988, and on its courtesy staff since 1988, and Newport Hospital since 1988.

Doctor Faintych was a member of the Rhode Island Medical Society, the Providence Medical Association, the American Psychiatric Association, and the Rhode Island Psychiatric Society.

Doctor Faintych was the husband of Bertha (Polacow) Faintych.

#### **John E. Farrell**

John E. Farrell, Executive Director of the Rhode Island Medical Society for 35 years before retiring in 1973, died May 28, 1990 at the age of 86.

Mr Farrell was also managing editor of the *Rhode Island Medical Journal* for many years. He initiated the Council of New England State Medical Societies and served as its secretary treasurer for five years. He was a former chairman of the Medical Society Executive Conference.

Mr Farrell was the husband of Mary E. (Boyle) Farrell.

#### **Fiorindo A. Simeone, MD**

Doctor Fiorindo A. Simeone, a professor emeritus of biological and medical science at Brown University and surgeon-in-chief emeritus at Miriam Hospital, died June 13, 1990 at the age of 82.

Doctor Simeone was a 1934 graduate of Harvard Medical School. He was a medical fellow of the National Research Council and had been on staff at Massachusetts General Hospital, Cleveland Metropolitan General Hospital, University Hospital-Cleveland, Highland View Hospital-Cleveland, and Miriam Hospital. He was on the consulting staff at Massachusetts Eye & Ear Infirmary, Rhode Island Hospital, Roger Williams General Hospital and the Veterans Administration Medical Center.

Doctor Simeone was an Army Medical Corps veteran of World War II, retiring as a colonel and had served in the North African and Mediterranean Theaters. He was an assistant professor of surgery and in genito-urinary surgery at Harvard Medical School from 1938 to 1950. He was a professor of surgery at Case Western Reserve University School of Medicine in Ohio and director of surgery at the City Hospital in Cleveland. He was a professor and

chairman of surgery at the American University of Beirut Medical School in 1960.

While demonstrating medical techniques in the Middle East in 1960, he performed the first two open heart operations ever done there. For his work he was made a Commander of the National Order of the Cedars of Lebanon, the highest honor a non-ruler can attain in the country. He served as a special assistant to the Governor of Rhode Island for Cancer Control and was a principal investigator, Rhode Island Cancer Control and Rehabilitation Program, National Cancer Institute, since 1974.

Doctor Simeone was a member of numerous national and regional societies. Among them the American Association for the Advancement of Science, American College of Cardiology, New York Academy of Sciences, American Medical Association, American College of Surgeons, and the American Association for Thoracic Surgery.

Doctor Simeone was the husband of Margaret M. (McLaren) Simeone.

#### **John R. Evrard, MD**

Doctor John R. Evrard, professor emeritus of obstetrics and gynecology at the Brown University Medical School, and director of medical education at Women & Infants Hospital before retiring in 1986, died July 6, 1990 at the age of 69.

Doctor Evrard graduated from Marquette University School of Medicine in 1944. In 1951, he received an MS in obstetrics and gynecology from Marquette. He

received his master's degree in public health from the University of California, Berkeley, in 1970, and moved to Providence to join the faculty at the Brown University Medical School. He served as professor of obstetrics and gynecology from 1982 to 1986. He was the associate director of ambulatory reproductive health services at Women and Infants Hospital from 1975 to 1986, and director of medical education from 1981 to 1986. A Navy veteran, Doctor Evrard served in the medical corps during the Korean War.

Doctor Evrard was the husband of Constance (Van Ert) Evrard.

#### **Samuel Pritzker, MD**

Doctor Samuel Pritzker, an anesthesiologist at Miriam Hospital for 35 years before retiring in 1974, died October 17, 1990 at the age of 85.

Doctor Pritzker was a 1931 graduate of Tufts University Medical School. During World War II, he served with the Army Medical Corps as chief of anesthesia for the 185th General Hospital in England, holding the rank of colonel.

He was a member of the American Medical Association, the Rhode Island Medical Society, the Providence Medical Association, and the Rhode Island and Massachusetts Societies of Anesthesiology. He was a diplomate of the American Anesthesiologists, and a fellow of the American College of Anesthesiologists. He was past chairman of the doctors division of the United Way.

Doctor Pritzker was the hus-

band of Ruth (Silverman) Pritzker.

#### **Paul A. Blackmore, MD**

Doctor Paul A. Blackmore, an obstetrician, died December 8, 1990 at the age of 71.

Doctor Blackmore graduated from Tufts Medical School in 1950 and had a private practice in Smithfield and Providence for 35 years before retiring in 1986. He was on the staff at Rhode Island Hospital, Women & Infants Hospital, St. Joseph Hospital, and Roger Williams General Hospital. He was an instructor in obstetrics at Tufts Medical School, and assistant obstetrics at Harvard Medical School.

He was a member of the American, Rhode Island, and Providence Medical Associations, the New England OBS-GYN Society, and the New England Society of Clinical Hypnosis. He was a former examiner for the National Board of Medical Examiners, and a member of Phi Chi Medical Fraternity. He was a medical officer for the Northeast Region Civil Air Patrol. He was a former president of the Medical Advisory Board, Smithfield Public Health League. He was a consulting surgeon for the Smithfield Police and Fire Department. He was a member of the Rhode Island Association for Retarded Children, the Governors Educational series on Mental Retardation, the Rhode Island Heart Association, and the American Cancer Society. He was an Army Air Corps veteran of World War II.

Doctor Blackmore was the husband of Elodie E. (Emin) Blackmore.

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## INFORMATION FOR AUTHORS

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**Specifications:** Manuscripts must be original typed copy (not all capitals) on 8½ × 11 inch firm typewritten paper, double-spaced throughout (including title page, text, acknowledgments, and references) with margins of at least one inch and using but one side of each page. Tables, charts, and legends should be submitted separately from the text, and referred to by number (ie, Fig. 1) within the text. Subheadings must be inserted at reasonable intervals to break the typographic monotony of the text. Pages must be numbered consecutively. Italics and boldface print are never used except as subheadings.

**Abbreviations:** The *Journal* attempts to avoid the use of jargon and abbreviations. All abbreviations, especially of laboratory and diagnostic procedures, must be identified in the text.

**Title Page:** All manuscripts must include a title page which provides the following information: (1) a concise and informative title; (2) the name of the author or authors with their highest academic degree (ie, MD, PhD); (3) a concise biographical description for each author which includes specialty, practice location, academic appointment, and primary hospital affiliation; (4) mailing address and office telephone of principal author; (5) mailing address of author responsible for correspondence or reprint requests; (6) source of support if applicable.

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